INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

ENVIRONMENTAL HEALTH CRITERIA 81

VANADIUM

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Published under the joint sponsorship of
the United Nations Environment Programme,
the International Labour Organisation,
and the World Health Organization

World Health Orgnization
Geneva, 1988

The International Programme on Chemical Safety (IPCS) is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. The main objective of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment. Supporting activities include the development of epidemiological, experimental laboratory, and risk-assessment methods that could produce internationally comparable results, and the development of manpower in the field of toxicology. Other activities carried out by the IPCS include the development of know-how for coping with chemical accidents, coordination of laboratory testing and epidemiological studies, and promotion of research on the mechanisms of the biological action of chemicals.

ISBN 92 4 154281 0

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NOTE TO READERS OF THE CRITERIA DOCUMENTS

Every effort has been made to present information in the criteria documents as accurately as possible without unduly delaying their publication. In the interest of all users of the environmental health criteria documents, readers are kindly requested to communicate any errors that may have occurred to the Manager of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda, which will appear in subsequent volumes.

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A legal file can be obtained from the International Register of Potentially Toxic Chemicals, Palais des Nations, 1211 Geneva 10, Switzerland (Telephone No. 988400 - 985850).

ENVIRONMENTAL HEALTH CRITERIA FOR VANADIUM

A WHO Task Group on Environmental Health Criteria for Vanadium met in Moscow, USSR from 30 March to 3 April 1987. Dr M.I. Gounar opened the meeting and greeted the members on behalf of the Centre for International Projects, Moscow, USSR. Dr E. Smith addressed the meeting on behalf of the three co-operating organizations of the IPCS (ILO/UNEP/WHO). The Task Group reviewed and revised the draft criteria document and made an evaluation of the health risks of exposure to vanadium.

The efforts of all those who helped in the preparation and finalization of the document are gratefully acknowledged.

* * *

Partial financial support for the publication of this criteria document was kindly provided by the United States Department of Health and Human Services, through a contract from the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA - a WHO Collaborating Centre for Environmental Health Effects. Financial support was also generously provided by the Institute of Occupational Health, Helsinki, Finland - an IPCS Participating Institution.

1. SUMMARY AND CONCLUSIONS

1.1 Identity, Physical and Chemical Properties, Analytical Methods

Vanadium (V) is a greyish metal that occurs in the form of two natural isotopes ^{50}V and ^{51}V. It forms oxidation states of -1, 0, +2, +3, +4, and +5, the oxidation states +3, +4, and +5 being the most common. Oxidation state +4 is the most stable. Vanadium pentoxide (V_2O_5) is the most common commercial form of vanadium. It dissolves in water and acids and forms vanadates with bases. Vanadium in the +3 oxidation state (e.g., V_2O_3) is basic and dissolves in acid forming a green hexa-aquo ion. Vanadium^{+3} salts are strong reducing agents. Organic compounds of vanadium are generally unstable.

Analytical methods have improved during recent years, and extremely small amounts of vanadium can be detected in various media. Atomic absorption assays are suitable for the routine determination of vanadium in different media. Some refractory oxides do not dissociate in flame. Sensitivity can be improved by the use of a high temperature oxyacetylene flame. Flameless atomic absorption for the determination of vanadium in air has a detection limit of 1 µg/litre. The same method can also be used for the determination of vanadium in water and biological samples, with a detection limit of 0.1 - 0.4 ng. Inductively coupled plasma optical emission spectrometry has proved an accurate and scientific development of atomic absorption.

Neutron activation analysis, which is both rapid and accurate, has been successfully used for the determination of vanadium in biological fluids, such as serum and blood, and in air, water, and biological materials. The quantitative separation of the components to be analysed is not necessary with this method. The detection limit of neutron activation assays is lower than that of atomic absorption methods, and vanadium in air can be determined at a level of 10^{-12} g.

Spark-source mass spectrometry is suitable for the simultaneous determination of several elements in air and biological materials and has a detection limit of 10^{-11} - 10^{-12} g. Neutron activation and spark-source mass spectrometry are sophisticated methods that, because of their high cost, are not always feasible. Various electrochemical and spectrophotometric assays are being widely used for the determination of vanadium in a variety of media. These methods have the advantage of being relatively cheap. Coulometric titration and controlled potential coulometry are accurate methods for the determination of vanadium in solutions. They are not as sensitive as the more sophisticated methods.

Stripping voltammetry and other modern modifications of polarography, as well as electrometrical methods based on catalytic reactions, are considered highly sensitive for the determination of vanadium in solutions and biological materials; however, depending on the composition of the sample, they could involve operations to separate out interfering elements.

1.2 Sources in the Environment, Environmental Transport and Distribution

Metallic vanadium does not occur in nature. Over 70

vanadium minerals are known, carnatite and vanadinite being the most important from the point of view of mining. Production of vanadium is linked with that of other metals such as iron, uranium, titanium, and aluminium. As rich minerals rarely occur in large deposits, ores with a low vanadium content, which exist in large amounts, are important. Extraction of vanadium from fossil fuels, including vanadium-rich oil and coal, tars, bitumens, and asphaltites, is important in several countries.

During the first half of the 1980s, the global production of vanadium (as vanadium pentoxide, V_2O_5) ranged from 34 to 45 million kg, China, Finland, South Africa, the USA, and the USSR being the biggest producers.

Vanadium is mainly (75 - 85%) used in ferrous metallurgy as an alloy additive in various types of steel. Its use in non-ferrous metals is important for the atomic energy industry, aircraft construction, and space technology. Vanadium is also widely used as a catalyst in the chemical industry, where vanadium pentoxide and metavanadates are especially important for the production of sulfuric acid and plastics. Small quantities of vanadium are used in a variety of other applications.

From the point of view of environmental pollution, power- and heat-producing plants using fossil fuels (petroleum, coal, oil) cause the most widespread discharge of vanadium into the environment. Burning of coal wastes or dumps of coal dust in mining areas are other sources of vanadium discharge into the atmosphere. In the distillation and purification of crude oil, most of the vanadium remains in the residues. Burning of distilled petroleum fuels contributes less vanadium to the atmosphere.

Emissions of vanadium may be high in the vicinity of large plants producing steel alloys. Vanadium is also released into the air: during the re-smelting of scrap steel and the transformation of titaniferrous and vanadic magnetite iron ores into steel; from the roasting of vanadium slags; from vanadium pentoxide smelting furnaces; and from electric furnaces in which ferrovanadium is smelted.

Most of the vanadium that enters sea water is in suspension or adsorbed on colloids. It does not react chemically with sea water and passes mechanically through it. This is reflected in its distribution on the sea bed in the form of silt. Only about 10% of the vanadium is present in a soluble form. The very low concentrations of vanadium in sea water indicate that vanadium is continuously removed from sea water, but the actual mechanisms are largely unknown. Vanadium that accumulates in ascidians, holothurians, and in marine algae will end up in the silt.

1.3 Environmental Levels and Human Exposure

Concentrations of vanadium in ambient air vary considerably. Elevated vanadium levels are believed to result from the burning of fossil fuels with a high vanadium content. Thus, heating requirements and seasonal differences in atmospheric inversions are reflected by fluctuations in vanadium levels in air. Air

levels of vanadium can be reduced by using distilled instead of residual fuel oil. In remote rural areas, levels are below 1 ng/m^3, but burning of fossil fuels can exceptionally increase local levels to about 75 ng/m^3. Typical concentrations in urban air vary over a wide range of about 0.25 - 300 ng/m^3. Large cities may have annual average air levels of the order of 20 - 100 ng/m^3, with markedly higher concentrations during the winter months compared with the summer months. In the vicinity of metallurgical industries, concentrations of 1 μg/m^3 are often found. Assuming an average air concentration of about 50 ng/m^3, about 1 μg of vanadium may enter the respiratory tract daily.

Vanadium concentrations in drinking-water are generally less than 10 μg/litre. A typical range is 1 - 30 μg/litre with an average of about 5 μg/litre.

The main source of vanadium intake for the general population is food. Reported vanadium concentrations in food tended to be higher in early studies compared with more recent measurements, which have shown concentrations in the range of 0.1 - 10 μg/kg wet weight, with typical concentrations of about 1 μg/kg. Recent estimates of daily intake suggest a range of 10 - 70 μg with the majority of estimates below 30 μg: higher estimates of up to 2 mg suggested in earlier studies were most likely due to analytical differences.

Exposure to high concentrations of vanadium in the air may occur in working environments. In the production of vanadium pentoxide, dust concentrations containing the pentoxide can range from 0.1 to 30 mg/m^3, and concentrations of about 0.5 - 5 mg/m^3 are not uncommon in the production of vanadium metal and vanadium catalysts. The highest vanadium concentrations in air occur in boiler cleaning where dust concentrations of 50 - 100 mg/m^3, but sometimes reaching 500 mg/m^3, have been encountered. Such dusts contain 5 - 17% of vanadium pentoxide and 3 - 10% of lower oxides. These levels are not representative of vanadium concentrations in the air in modern plants, where levels are usually much lower.

1.4 Kinetics and Metabolism

The rate of pulmonary absorption of various vanadium compounds has not been determined, but it has been estimated that about 25% of soluble vanadium compounds may be absorbed. The results of experimental animal studies have shown complete clearance of the relatively soluble vanadium pentoxide from the lung in 1 - 3 days following acute exposure. When $^{48}VOCl_3$ was instilled intratracheally in the rat lung, 50% was cleared within the first day; 3% remained after 63 days.

Vanadium salts are poorly absorbed from the human gastrointestinal tract, only 0.1 - 1% of the very soluble oxytartarovanadate being absorbed. A very low level of gastrointestinal absorption has also been seen in animal studies, and, though it has been shown that soluble vanadium compounds may be absorbed through the skin of rabbits, the dermal absorption of vanadium compounds is likely to be extremely small.

Absorbed vanadium is mainly transported in the plasma.

Vanadium concentrations in all tissues are generally low, but are higher in the liver, kidney, and lung than in other tissues. Levels in the liver may be in the range of 4.5 - 19 μg/kg wet weight and those in kidney, 3 - 7 μg/kg. Higher levels may be found in lung tissue with mean concentrations ranging from 10 to 130 μg/kg wet weight. Small amounts have been found in the placenta, and vanadium passes through into the membranes rather than the fetus. Vanadium is present in breast milk and saliva. It also passes through the blood-brain barrier. Reported levels in human blood differ widely, levels in whole blood and serum lying within the range of 0.01 - 0.4 mg/litre. Most studies have shown levels below 0.1 mg/litre.

Because of the low level of absorption in the gastro-intestinal tract, ingested vanadium is mainly eliminated unabsorbed with the faeces. The principal route of excretion of absorbed vanadium is through the kidneys. Vanadium concentrations in urine are of the order of 0.1 - 0.2 μg/litre. The majority of studies on occupationally exposed populations have shown a poor correlation between vanadium concentrations in air and the amounts excreted in urine. However, in very highly exposed workers, urine-vanadium levels increased 20 - 30 times over a work-shift.

1.5 Effects on Experimental Animals and *In Vitro* Test Systems

Vanadium is an essential element for chicks and rats. Vanadium deficiency in these species causes reduced growth, impairment of reproduction, and disturbance of the lipid metabolism. Vanadium has a diuretic and natriuretic action in rats and inhibits the Na^+-K^+-ATPase (EC 3.6.1.3) in microsomal fractions of kidney, brain, and heart of several species. The observation of the inhibiting effects on Na^+-K^+-ATPase led to the discovery that a variety of enzymes are vanadium sensitive. For instance, ATP phosphohydrolase, ribonuclease, adenylate-kinase, phosphofructokinase, and glucose-6-phosphatase are inhibited by vanadium compounds.

In general, vanadium is better tolerated by small animals, such as the rat and mouse, than by larger animals including the rabbit and horse. The toxicity of vanadium is low when administered orally, moderate when inhaled, and high when injected. A 1-h LC_{50} of 70 mg/m^3 has been reported for the inhalation of vanadium pentoxide in the rat. The minimum concentration of vanadium pentoxide that caused mild signs of acute poisoning in the rat was 10 mg/m^3 air. Exposure of rabbits to vanadium pentoxide at 205 mg/m^3 resulted in conjunctivitis and tracheitis, pulmonary oedema, bronchopneumonia, and death within 7 h. The exposure of rats for 2 h every other day for 3 months to 3 - 5 mg/m^3 caused pathological changes only in the lungs. The endothelium was swollen, there was capillary congestion, perivascular oedema, and small haemorrhages indicating altered vascular permeability. Similarly, respiratory symptoms, such as nasal discharge, sneezing, dyspnoea, and asthmatic reactions, were seen in rabbits exposed to vanadium trioxide aerosol at 40 - 75 mg/m^3, for 2 h/day over 9 - 12 months.

The effects of acute and long-term inhalation exposure on the respiratory tract may partly be due to the effect of vanadium on the macrophages. A 50% reduction in the viability of cultured rabbit macrophages was seen after exposure to 13 μg vanadium/ml (as vanadium pentoxide) for 20 h. Exposure for 2 h (vanadium pentoxide) reduced the viability of murine pulmonary alveolar macrophages at a dose of 7 μg vanadium/ml.

Vanadium pentoxide administered in the diet at 0.05 - 0.5 mg vanadium/kg, per day, for 80 days, caused impairment of conditioned reflexes in the rat. Daily parenteral injection of sodium metavanadate (3.2 μg/kg body weight per day, for 10 - 15 days) increased the reactivity of cytochrome oxidase in guinea-pig brain, whereas a dose of 128 μg/kg per day did not induce any effects and 5.12 mg/kg body weight per day reduced the activity. Cholinesterase activity in the rat brain was reduced by the intraperitoneal administration of 1 - 10 mg vanadyl sulfate/kg.

Fatty changes with partial cell necrosis of the liver occurred in rats and rabbits exposed by inhalation to vanadium pentoxide, trioxide, or trichloride (10 - 70 mg/kg, 2 h/day, for 9 - 12 months). Fatty changes in the liver of rats also occurred after exposure to ammonium vanadate.

Vanadate has a diuretic and natriuretic effect on rat kidneys, but not on those of the dog or cat. This effect is thought to be due to the inhibition of Na^+-K^+-ATPase, which, in turn, inhibits the tubular reabsorption. Fatty changes in the myocardium of both the rat and rabbit were seen after long-term inhalation of vanadium pentoxide, trioxide, or trichloride (10 - 70 mg/m^3, 2 h/day, for 9 - 12 months). Perivascular swelling of the myocardium was also seen.

Rats given metavanadate subcutaneously (0.85 mg/kg body weight) showed shedding of spermatogenic epithelium. Gonadotoxic effects were suggested by the absence of fertilization of female rats by male rats that had been exposed subcutaneously to vanadium at 0.85 mg/kg body weight. The same dose administered to female rats on the fourth day of pregnancy increased the mortality of embryos.

Parenteral administration of ammonium vanadate (intraperitoneal) to pregnant Syrian golden hamsters and of vanadium pentoxide (subcutaneous and intravenous) to pregnant rats

resulted in increased numbers of fetal deaths and significantly increased skeletal abnormalities. These studies indicate a possible teratogenic effect of vanadium.

There are few data on the mutagenicity and carcinogenicity of vanadium compounds and limited indications of the mutagenicity of vanadium. In a rec assay with *Bacillus subtilis*, testing DNA damaging capacity, three compounds ($VOCl_2$, V_2O_5, NH_4VO_3), gave mildly positive results, while results of tests in *Escherichia coli* and *Salmonella* strains were mostly negative. Bacterial assays have given conflicting results and no firm conclusions can be drawn.

No information is available indicating a carcinogenic action of vanadium.

1.6 Effects on Man

No data are available on the effects of vanadium deficiency in man, and, though possible regulatory roles of vanadium have been suggested, a daily dietary requirement of vanadium for man has not been defined.

1.6.1 Local effects and dose-response relationships

There are comparatively few reports about the effects of vanadium exposure on the skin. Eczematous dermatitis has been reported in workers exposed to vanadium pentoxide, with dust levels as low as 6.5 $\mu g/m^3$.

Inhalation of vanadium pentoxide produces local irritation. The exposure of 2 volunteers to 1 mg/m^3 for 8 h resulted, 5 h later, in coughing that lasted for 8 days. Inhalation of 0.2 mg/m^3 by 5 volunteers resulted in similar symptoms, i.e., coughing that started a little later (20 h after exposure) and lasted for 7 - 10 days. Similar irritation was noted in 2 volunteers exposed to 0.1 mg/m^3 for 8 h. A dose-response relationship was observed when 11 volunteers were exposed to 0.4 mg vanadium pentoxide/m^3 condensation aerosol. Tickling and itching with dryness of the mucous membranes of the mouth were reported by 5 subjects at 0.16 mg/m^3, whereas, at 0.08 mg/m^3, none of the subjects noted any effects.

Workers exposed to dust containing vanadium at 0.01 - 0.04 mg/m^3, for about 10 months, showed irritant effects on the mucous membranes of the upper respiratory tract. Cough, increased production of sputum and irritation of the eyes, nose, and throat occurred among workers exposed to a maximum of 0.9 - 5 mg vanadium/m^3. At high exposures (dust concentrations ranging between 5 and 150 mg/m^3), workers developed atrophic rhinitis, and chronic bronchitis. Blood-stained sputum, haemoptysis, and bronchospasm were seen in a proportion of those exposed. In workers exhibiting asthmatic reactions, when exposed to vanadium pentoxide, there was no indication of specific sensitization; the mechanism is thought to be a direct chemical one.

Among the local effects caused by vanadium exposure, the green tongue occurring in a proportion of the exposed is considered a sign of exposure rather than a toxic effect.

1.6.2 Systemic effects and dose-response relationships

The effects of vanadium on dental caries is a debatable issue. It has been claimed that, when added to the diet of hamsters, vanadium had a favourable effect on dental caries. It has also been shown, in one report, that the application of an ammonium salt of vanadium reduced caries in children. However, other studies between 1955 and 1968 failed to demonstrate such beneficial effects of vanadium, and in one study, an increase in caries was observed after administration of vanadium in the drinking-water at 2 mg/litre.

The effects of vanadium on cholesterol levels have not been fully elucidated. Studies in the 1950s and 1960s claimed a temporary drop in cholesterol levels in patients fed ammonium oxytartarovanadate and ammonium vanadyltartrate, for several weeks, at 50 - 200 mg/day. Although some data on experimental animals have indicated that vanadium reduces cholesterol levels, this has not been convincingly shown in human beings.

The results of studies on the effects of vanadium pentoxide on rats have shown a decrease in cysteine in hair and also a reduction of co-enzyme A in the liver, which could explain the mechanism behind the reduction of cysteine. Data on the effects of vanadium on haematopoiesis are inconsistent, and it has not been possible to assess the effects of low-level vanadium exposure on iron metabolism. Vanadium has been shown to inhibit the Na^+-K^+-ATPase (EC 3.6.1.3) in human red blood cells.

Systemic effects are rare in workers exposed to vanadium compounds. Nonspecific signs and symptoms including headache, weakness, nausea, vomiting, and ringing in the ears have been reported, and there have been reports of dizziness or giddiness and neuraesthenic and vegetative symptoms. A few early reports mention tremor. It is not possible to derive dose-response relationships for these effects on the nervous system. They are likely to be associated only with fairly high exposure levels. Systemic effects such as anaemia, leukopenia, and basophilic granulation of leukocytes have been reported, but cannot be expressed in relation to any particular exposure level. Although fatty changes in the liver and kidney have been seen in experimental animals, there are no data on human beings to evaluate these effects.

In exposed workers, palpitations of the heart at rest and on exercise have been reported. Transient coronary insufficiency and a high incidence of extrasystoles have also been reported. The association between these symptoms and vanadium is doubtful. Low-level exposure of workers to vanadium pentoxide at 0.01 - 0.04 mg/m^3 air for about 10 months, preceded by exposure to 0.2 - 0.5 mg/m^3 for about 11 years, did not cause any pathological effects on the blood picture, the cysteine level in hair, or the respiratory function. Wheezing was more common in exposed workers than in controls.

A few attempts to relate vanadium levels in ambient air to adverse effects on the general population have been made. Positive correlations between mortality from cardiovascular disease, lung carcinoma, and bronchitis, and vanadium air concentrations have been reported, but, so far, causal associations have not been reported. Further studies on the possible effects of vanadium exposure on the general population are needed, with better control of confounding factors and various intercorrelations than that in available studies.

1.7 Evaluation of Health Risks for Man

There is no convincing evidence that vanadium is an essential element for man. Vanadium interferes with a multitude of biochemical processes, and its physiological role should be

carefully assessed. Vanadium penetrates the blood-brain barrier and is present in breast milk. Effects on the fetuses of rats and hamsters when vanadium was administered to pregnant animals indicate transfer across the placental barrier; however, Vanadium appears to concentrate in the membranes rather than in the fetus.

Current levels of vanadium in the ambient air have been associated with mortality in the general population due to various diseases of the heart and lung. All studies reporting such relationships have had serious flaws, and no causal relationships between vanadium and disease in the general population have been established.

Practically all the information on adverse effects on human beings has been derived from controlled, therapeutic, or occupational exposure to concentrations that do not occur under normal conditions. Exposed workers may suffer from irritation of the eyes and the respiratory tract. There is a dose-response relationship between the concentration of vanadium in air and its irritant effects. With short-term inhalation exposure to vanadium pentoxide at a concentration of about 0.1 mg/m^3, irritation is manifested as coughing with increased production of mucous. Continuous exposure to even lower levels (0.01 - 0.04 mg/m^3) may cause some irritation, but does not impair lung function. A reversible decrease in forced vital capacity (FVC) has been reported with exposure to a dust containing 15% vanadium at a level of about 0.5 mg/m^3. High exposure levels of 5 - 150 mg/m^3 cause atrophic rhinitis and bronchitis with a risk of bronchospastic effects. Eczematous dermatitis may occur with low-level exposure to vanadium pentoxide (6.5 $\mu g/m^3$).

Non-specific effects, such as headache, nausea, weakness, ringing in the ears, and palpitation, have been reported in exposed workers. These effects have not been related to any specific exposure level, but, on such occasions, it has been in the mg/m^3 air range. Such symptoms may be taken as an indication of the need for personal protection in work tasks associated with the risk of heavy exposure to dusts containing vanadium.

Several reported effects of vanadium need further research, including the effects on cholesterol levels, iron metabolism, and haematopoiesis. Available data do not imply any risk of carcinogenic effects; however, the data cannot be considered conclusive. There are only weak indications of possible mutagenic effects of vanadium compounds. The results of studies on point mutations in bacteria are conflicting, and there are too few studies to draw definite conclusions with respect to mutagenicity. The scanty evidence of spermato- and gonadotoxic effects needs corroboration. The available data suggest that vanadium may be embryotoxic and gonadotoxic. However, the results indicating the induction of teratogenicity require further confirmation.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1 Identity

Vanadium (V) is a greyish ductile metal with an atomic number of 23, an atomic mass of 50.942, a melting point of 1890 ± 10 °C, a boiling point of 3380 °C at 1 atm (1.013×10^5 Pa), and a specific gravity of 6.11 at 18.7 °C (Weast, 1986-87). Vanadium has two natural isotopes, ^{50}V and ^{51}V, and several radioactive isotopes ($^{46-49}V$, $^{52-54}V$) have been obtained artificially (Clark, 1975; Weast, 1987).

2.2 Physical and Chemical Properties

Vanadium has a maximum oxidation state of +5. Compounds of vanadium may contain vanadium in oxidation states of -1, 0, +2, +3, +4, and +5. Vanadium is usually found bound to oxygen as a negatively charged polymeric oxyanion that tends to complex to polarizable ligands, such as phosphorus and sulfur (Buckingham, 1973; Cotton & Wilkinson 1980).

Vanadium's ability to be either an electronegative or an electropositive metal results in a great variety of chemical compounds (vanadium is second only to carbon in the number of chemical compounds). Physical properties of some important compounds are shown in Table 1 (Weast, 1987).

Vanadium usually occurs in the pentavalent state. Pentavalent vanadium is stable in aqueous solutions over a wide range of pH.

The formation of isopoly and heteropoly compounds is most characteristic of pentavalent vanadium in aqueous solutions. The tendency of vanadium compounds to form V-0-V-0 linkages is due to the electronegativity of vanadium and to electronic hybridization (Zolotavin, 1954).

Vanadium pentoxide (V_2O_5), the most common commercial form of vanadium, dissolves in water (8 g/litre) to give a pale yellow acidic solution containing vanadium species that are moderately strong oxidizing agents (Cotton & Wilkinson, 1962).

Vanadium^{5+} is reduced to vanadium^{4+} by relatively mild reducing agents. The 4+ state is the most stable oxidation state for vanadium. Nearly all of the complexes of vanadium4+ are derived from the vanadyl ion (VO_2^+). Most of these complexes are anionic and a few are non-electrolytes. Vanadium in this oxidation state forms a large number of five or six coordinate complexes, such as vanadyl acetylacetonate and vanadyl porphyrins found in crude petroleum.

Vanadium^{3+} (e.g., V_2O_3) is completely basic and dissolves in acid to give the green hexa-aquo ion $(V(H_2O)_6)^{3+}$. Vanadium^{3+} is a strong reducing agent that slowly attacks water with the liberation of hydrogen and the production of vanadium^{4+}. The hexa-aquo ion of vanadium is easily oxidized to vanadium^{4+}.

Table 1. Physical properties of some vanadium compounds

Compound	Melting point (°C)	Boiling point (°C)	Solubility in water (g/litre) Cold	Hot

Vanadium[a] pentoxide	690	1750	0.7[b]	no data
Vanadium[a] trioxide	1970	no data	slightly soluble	soluble
Sodium[a] metavanadate	630	no data	211	388
Vanadium tetrachloride[a]	-28 ± 2	148.5	decomposes	no data
Vanadium oxychloride[a]	no data	127	decomposes	no data
Ammonium vanadate[a]	200[c]	no data	5.2	69.5[c]

[a] From: Weast (1987).
[b] From: Cotton & Wilkinson (1980).
[c] Decomposes.

2.3 Analytical Methods

A review of analytical methods used to determine vanadium in different media suggests that atomic absorption and spectrophotometric assays are the most suitable for routine analysis. Neutron activation analysis has been widely and successfully used for the determination of vanadium in serum and blood.

2.3.1 Atomic absorption analysis and emission spectrometry

Atomic absorption techniques have been most widely used for the determination of vanadium in various media. Vanadium forms heat-stable refractory oxides that are not completely dissociated in a flame. The use of a high temperature oxyacetylene flame improves the sensitivity of the method (L'vov, 1970). Other ways of improving sensitivity have been suggested (Christian & Feldman, 1970; Omang, 1971; Kragten, 1981; Wood et al., 1982). High sensitivity has been achieved using flameless electrothermal AAS assays with a graphite furnace. A flameless atomic absorption method using a graphite furnace was recommended by NIOSH (1977) for the determination of vanadium in air. A detection limit of 1 ng/ml for a maximum sample injection of 100 µlitre was given, corresponding to an absolute sensitivity of 0.1 ng of vanadium. A detection limit of 0.4 ng was reported by Hwang et al. (1972) using a flameless atomic absorption method that was applicable to air, water, and biological samples.

A method for the determination of vanadium in work-place air using direct current plasma atomic emission spectrometry (DCP-AES) was reported by Pyy et al. (1983). A detection limit for vanadium in air of 0.004 mg/m^3 and a practical working range of 0.01 - 100 mg/litre were suggested. The precision was given as 1%. The results of this assay correlated with those obtained

with both flame (FAAS) and electrothermal atomization (EIA-AAS) atomic absorption spectrometry.

Vanadium and 11 other trace elements in natural water were determined using AAS and the stabilized temperature platform furnace. A detection limit of 0.6 µg/litre with a precision of 10 - 15% was achieved (Manning & Slavin, 1983).

Electrothermal AAS methods have been used to determine vanadium in urine. Buchet et al. (1982) detected concentrations in the range of 1 - 500 µg/litre, giving a coefficient of variation for triplicate samples of less than 8% for 10 µg vanadium/litre. A practical detection limit for vanadium in urine of 2 µg/litre was reported by Pyy et al. (1984) also using an electrothermal AAS method with a graphite furnace. Extraction of vanadium with ammonium 1-pyrrolidine-carbodithioate into 4-methylopentan-2-one reduced the detection limit to 0.5 µg/litre.

Atomic absorption is widely used for the determination of vanadium in biological materials, such as tissues and serum. A detection limit of 30 pg and a sensitivity of 65 pg have been reported using a flameless apparatus and graphite tubes (Stroop et al., 1982).

AAS methods can also be used in the determination of vanadium in other media such as crude petroleum (Wood et al., 1982) and sewage sludge (Kempton et al., 1982). Improved techniques have been developed (Barbooti & Jasim 1982; Slavin et al., 1983) including the use of simultaneous AAS and mass spectrometry (Styris & Kaye, 1982).

In general, emission spectral analysis has been considered less accurate than colorimetric methods (Bagget & Huyck, 1959; Sandell, 1959). However, it is a universal selective method by which small amounts of vanadium can be determined in the presence of numerous other elements. The relative sensitivity of spectral analysis is 10^{-3} - 10^{-5}%. Sensitivity can be increased by prior separation of the element to be determined.

Inductively coupled plasma optical emission spectrometry has been used for the simultaneous determination of several elements in aerosol samples collected with cascade impactors (Broekaert et al., 1982) and also for the determination of vanadium in urine (Barnes et al., 1983).

2.3.2 Neutron activation analysis

Neutron activation analysis is more rapid and accurate than other methods. Using this method, it has been possible to determine up to 70 elements in amounts of 10-12 g in air (Dams et al., 1970; Gershkovich & Stykan, 1972). In carrying out neutron activation analysis, a weighted sample or test solution is irradiated with a thermal neutron flux in an atomic reactor, for a certain length of time (Flaherty & Eldrige, 1970; Frolov, 1970). During irradiation, one or several isotopes of the element being tested are formed. The activity of the isotopes formed is determined from the gamma peak by means of a scintillation gamma spectrometer. The sensitivity of the method depends on many factors including: size of the particle flux,

duration of sample irradiation, efficiency of the counter, time elapsed since the beginning of irradiation, background response of the counter, etc.

The chemical form of vanadium in water can be determined using a ^{48}V tracer and neutron activation (Orvini et al., 1979).

Neutron activation determination of vanadium in biological material is complicated by the high concentration of sodium, even when a Ge/Li detector is used. Because of the short life of the isotope, the sodium must be eliminated before irradiation, normally by absorption on antimony pentoxide (Ralston & Sato, 1971). Neutron activation has been successfully used to determine vanadium in serum (Byrne & Kosta, 1978; Sabbioni et al., 1979; Cornelis et al., 1980, 1981) and body tissues (Yukawa et al., 1980).

2.3.3 Spark-source mass spectrometry

Spark-source mass spectrometry is an excellent analytical tool (Johnson et al., 1974). The absolute sensitivity of the method is 10^{-11} - 10^{-12} g, and the relative sensitivity is 10-7 g-atom. Up to 70 elements can be recorded simultaneously on the photographic plate and only a few milligrams of sample are needed (Chupahin et al., 1972). This method is used for the multi-element analysis of air and biological materials.

Evans & Morrison (1968) described the problems that occur in analysing ashed biological material for vanadium using spark-source mass spectrometry. The ash must be completely free of organic mixtures, since vanadium belongs to the class of elements in which inorganic compounds are completely bound to biological material. The concentration of vanadium found by spark-source mass spectrometry was 10 times as high as that found by the spectral method in the same samples.

Vanadium levels in urine and biological tissues were determined by Pilz & Komischke (1972) using salicylhydroxamic acid. The vanadium complex was extracted with N-pentanol, and the vanadium was determined in the extract by spectrophotometry.

Beer's law was observed, with concentrations of vanadium ranging from 1 to 2000 µg/25 ml extract. There was no interference by cobalt, nickel, zinc, molybdenum, tungsten, iron, calcium, lead, or chromium.

2.3.4 Spectrophotometric analysis

Organic reagents are often used to improve the specificity of spectrophotometric analysis. Over 80 organic reagents have been suggested for the direct quantitative determination of vanadium (Mustafin et al., 1969; Muzquin et al., 1981). The specificity of the organic reagents can be increased when complexing agents are used to bind the interfering ions. In most cases, particularly those based on complexing reactions, specificity and sensitivity are enhanced by prior separation of vanadium, mostly by extraction. Acyl derivatives of hydroxylamine containing the OC-NOH group show high selectivity for pentavalent vanadium, when the product of interaction in a

highly acid medium is extracted (Tandon & Bhattacharya, 1961; Majumdar & Das, 1965).

Spectrophotometric analysis based on catalytic reactions, e.g., on acceleration of the oxidation of aromatic amines and aminophenols with chlorates, bromates, periodates, and persulfates in the presence of pentavalent vanadium compounds, is widely used to determine trace amounts of vanadium (Bakal & Liseckaja, 1971; Zheljazkova et al., 1972). The sensitivity of kinetic methods is theoretically unlimited and their use for analysing biological materials is quite promising, because of the considerably reduced amounts of material needed for analysis (Jacimirskij, 1967).

Welch & Allaway (1972) proposed a method to determine nanogram quantities of vanadium by means of an acid oxidation reaction catalysed by vanadium pentoxide. Christian (1971) determined vanadium in blood and urine using a method based on the catalytic effect of vanadium on the oxidation reaction of phenylehydrazine-N-sulfonic acid with potassium chlorate. Vanadium concentrations of 0.056 ± 0.033 mg/litre in blood-plasma, 0.061 ± 0.019 mg/litre in red blood cells, and 0.022 ± 0.015 mg/litre in urine were detected using this method.

2.3.5 Electrochemical methods

Vanadium is commonly determined by electrochemical methods, namely by volumetric titration with electrometric detection, such as potentiometry (Cassani, 1968), amperometry (Singh & Sharma, 1970), as well as by coulometric titrations (Kostromin et al., 1970), polarography (Shevchenko & Gorodynskij, 1964; Budnikov & Medjantseva, 1973), and coulometry (Rigdon & Harrar, 1969). Catalytic reactions with polarographic, potentiometric, and amperometric detection (Weisz et al., 1974) are also used.

Stripping voltammetry (Van den Berg & Huang Fi Qiang, 1984) and other modifications of polarography (Veys, 1983), as well as electrometric methods based on catalytic reactions are highly sensitive but, depending on the composition of the sample, they can involve operations to separate out interfering elements in the sample. The selectivity of controlled potential coulometry is high, making the separate determination of vanadium compounds of different valencies possible. The introduction of differential techniques into both coulometric titration and controlled potential coulometry results in very high accuracy (Agasyan et al., 1975; Shkolenok et al., 1977).

2.3.6 Chromatography

The chromatographic method has found little practical application in determining trace quantities of vanadium though Bonig & Heigener (1971) used selective paper chromatography to determine microgram quantities of vanadium.

3. SOURCES IN THE ENVIRONMENT, ENVIRONMENTAL TRANSPORT AND DISTRIBUTION

3.1 Natural Occurrence

3.1.1 Rocks

Vanadium is a typical rare element, present in the earth's crust at concentrations of around 0.015 g/kg, which is roughly in the same proportions as chromium, strontium, and zirconium. It is considerably more widespread than copper, lead, zinc, and other minor elements. Some 70 vanadium minerals are known, of which 40 are vanadates. The main vanadium minerals are vanadinite (19% vanadium pentoxide), descloizite (220 g/kg), cuprodescloizite (170 - 220 g/kg), carnotite (200 g/kg), roscoelite (210 - 290 g/kg), and patronite (170 - 290 g/kg). Admixtures are found in the ore minerals titaniferromagnetite (up to 88 g vanadium pentoxide/kg), magnesioferrite (160 g/kg), magnetite (6 g/kg), rutile (1 g/kg), and ilimenite (4 g/kg). Metallic vanadium does not occur in nature, and the richer minerals rarely occur in large deposits. Vanadium compounds are present in fossil fuels (oil, coal, shale), and some oilfields have a high vanadium content (NAS, 1974).

Vanadiferrous phosphorites (1 - 10 g/kg), asphaltites (up to 500 g/kg in ash), and titaniferrous magnetite placers, mainly of the sea-beach type (about 3 g/kg), are important sources of vanadium. Oolite brown iron ore (ferrophosphorous ore), which contains only small amounts of vanadium pentoxide (0.7 - 2 g/kg) but occurs extensively, carbonaceous cherts (15 - 20 g/kg), bauxites (0.2 - 0.4 g/kg), the ash of coal and combustible shale (2 g/kg), and ferromanganese nodules in the ocean, may all provide sources for vanadium extraction (Todria, 1963; Holodov, 1968, Schumann-Vogt, 1969; Borisenko, 1973; Rose, 1973; NAS, 1974). The most important deposits of vanadium ores are found in Canada, Finland, Namibia, South Africa, Sweden, the USA, the USSR, and Zambia (Borisenko, 1973).

3.1.2 Soils

The vanadium contents of soils are related to those of the parent rocks from which they are formed and range from 3 to 310 mg/kg, the highest concentrations being found in shales and clays (Waters, 1977). Vanadium is evenly distributed in the soil horizons, but there is sometimes a higher level in the A horizon, possibly connected with the vital activity of plants. In the neighbourhood of vanadium-bearing rocks or of large amounts of iron oxides, a moderate local increase in soil-vanadium levels may be found. Vanadium is present in the soils of France, Japan, Spain, the United Kingdom, and the USA at levels that are partly determined by the distribution of iron in these soils (Holodov, 1968); levels ranged from 1 to 680 g/kg (Vinogradov 1957). The lowest concentration was reported from Japan, and the highest from Spain. Vinogradov (1957) found lower vanadium concentrations in USSR podzols than in tundra and chernozem soils.

3.1.3 Water

The levels of vanadium in fresh water in different parts of the world vary from undetectable to 0.220 mg/litre (Table 2).

The geographical differences in fresh water vanadium levels are due to differences in rainwater runoff from natural sources or in industrial effluent. Data on vanadium levels in waters contaminated with industrial effluent are presented in section 3.4.1. Some data on vanadium in sea-water are presented in Table 3.

3.1.4 Air

Natural sources of airborne vanadium are marine aerosols and continental dust. The concentration of vanadium in the air at the South Pole is very low (0.001 - 0.002 ng/m^3) (Zoller et al., 1974). Levels in ocean air in the middle latitudes are about two orders of magnitude higher (Hoffman et al., 1972; Martens et al., 1973).

Atmospheric concentrations of vanadium from continental dust and sea spray can be predicted using various models (NAS, 1974). Concentrations of 0.1 ng/m^3 (range, 0.02 - 0.8 ng/m^3) measured over the eastern Pacific Ocean and 0.72 ng/m^3 (range, 0.21 - 1.9 ng/m^3) over rural northwestern Canada agree with these predictions, and can be regarded as natural background levels. Many rural areas in the USA display similar or only slightly higher levels. However, in northeastern USA, rural air concentrations are higher, ranging from 2 to 64 ng/m^3, and are attributed to the local burning of fuel oil with a very high vanadium content (section 4.1.1).

Only small amounts of airborne vanadium are produced as a result of volcanic action (Zoller et al., 1973).

3.1.5 Plants

Vanadium occurs in small amounts in all plants, usually at concentrations of a few mg/kg dry weight. Within a given species, variation is influenced by soil-vanadium levels, soil acidity, and growing conditions, but the range of variation is not large. The vanadium concentrations in roots are nearly the same as the level in the soil in which they are grown. Vanadium levels are lowest in the aerial portions of most plants and are unrelated to soil levels. Bertrand (1950) found vanadium in each of 62 plant species analysed; mean concentrations in higher plants were 0.16 mg/kg fresh weight, 1 mg/kg dry weight, and 7 mg/kg ash. A mean level of 1.2 mg/kg was found in the leaves of woody plants by Hanna & Grant (1962).

Vanadium accumulation occurs in the fly agaric mushroom *(Amanita muscaria)*, which contains about 100 times as much as other mushrooms or plants (Bertrand, 1950). Cowgill (1973) determined vanadium concentrations in fresh-water plants in the range of 0.4 - 80 mg/kg. The higher value of 80 mg/kg was found in the pickerel weed *(Pontedaris cordata)*, which is a probable accumulator. Mosses *(Hypnum cupressiforme)* also accumulate vanadium; concentrations of about 10 mg/kg have been measured in rural mosses, whereas concentrations may be as high as 50 - 250 mg/kg in mosses from city areas (Tyler, 1970; Ruhling, 1971).

Table 2. Vanadium levels in fresh water

Source of water	Vanadium level	Reference
Japan		
Rivers of Japan	0.001 mg/litre	Sugawara et al. (1956)
Waters of 5 Japanese lakes	0.0001-0.087 mg/litre (average, 0.0007 mg/litre)	Sugawara et al. (1956)
USA		
Rivers of Colorado	0.2 - 49.2 µg/litre	Linstedt & Kruger (1969)
Rivers of New Mexico	up to 19 µg/litre	NAS (1974)
Rivers of the USA	0.001 mg/litre	Durum & Haffty (1963)
Rivers of the Colorado plateau	to 70 µg/litre	Schroeder (1970a)
Wyoming River	30 - 220 mg/litre	Schroeder (1970a)
USSR		
30 large rivers	traces to 0.43 mg/litre average 0.037 mg/litre; average in dissolved form, 0.0012 mg/litre	Konovalov et al. (1968)
Protva and Tarusa Rivers	0.007-0.0135 mg/litre	Tjurjukanov (1963)
Moscow River	0.0025-0.0074 mg/litre	Tjurjukanov (1963)
Rivers of the Klinsk-Dmitrovsk ridge	0.005-0.0074 mg/litre	Tjurjukanov (1963)
Waters of the area west of the Kama River in the Tartar ASSR: rivers and lakes	0 - 34 µg/litre	Petuhov et al. (1969)
Uzbek SSR: surface waters	0.0003 - 0.003%	Mirzaeva (1965)

Table 3. Vanadium levels in Sea-water[a]

Water	Vanadium level (mg/litre)	Reference
Sea-water	0.0005 (average)	Vinogradov (1944)
Sea-water	0.0003	Sverdrup et al. (1950)
Near the Japanese coast	0.001 - 0.002	Sugawara et al. (1956)

Sea-water	0.002	Goldberg (1961)
Western Pacific	0.003	Sugawara et al. (1956)
Sea-water	0.002 - 0.029	NAS (1974)

[a] Modified from: Holodov (1968).

3.1.6 Animals

Vanadium appears to be present in all animals, but tissue levels in most vertebrates (especially land mammals) are so low that detection is difficult. Higher concentrations have been found in marine species, especially invertebrates (Bertrand, 1950). In land mammals, the highest levels occur in the liver and skeletal tissues.

Estimates by Vinogradov (1959) and Schroeder (1970a) of vanadium concentrations in animals are shown in Table 4. Limited data for several tissues of wild animals are shown in Table 5, and some concentrations in domestic animal tissues, measured by sensitive methods, are given in Table 11 (section 4.1.3.1). On the whole, these agree with Bertrand's observations.

Using neutron activation analysis, Fukai & Meinke (1962) reported that concentrations of vanadium in the soft tissues of fish were 1000 times those in seaweeds and molluscs. The highest concentrations of vanadium in marine organisms have been found in certain ascidians (sea squirts) (e.g., *Phallusia* mamillata , 1900 mg/kg), certain holothurians (sea cucumbers) (e.g., *Sticopus mobii* , 1200 mg/kg), a mollusc *(Pleurobranchus* plumula , 150 mg/kg), and marine algae.

Table 4. Vanadium levels in animals[a]

Animal	Vanadium concentration (mg/kg dry weight)
Coelenterate	2.3
Annelid	1.2
Mollusc	0.7
Echinoderm	1.9
Crustacean	0.4
Insect	0.15
Fish	0.14
Mammal	0.4

[a] From: Vinogradov (1959) and Schroeder (1970a).

Table 5. Vanadium levels in tissues of wild animals[a]

Tissue[b]	Number of samples	Vanadium concentration (mg/kg wet weight) Mean	Range
Kidney	4	0.94	0 - 2.07
Liver	4	0.25	0 - 0.94
Heart	4	1.16	0 - 3.40
Spleen	1	1.16	

[a] From: Schroeder (1970a).
[b] Beaver, deer, woodchuck, rabbit, muskrat, and fox.

In certain ascidians, trivalent vanadium is present as a chromoprotein called haemovanadin together with sulfuric acid in green cells termed vanodocytes; in other forms, the free haemovanadin is present in plasma (Hudson, 1964).

3.2 Man-Made Sources

3.2.1 Production levels and processes

The annual production of vanadium (as vanadium pentoxide) ing 1980-84 was between 34 and 46 million kg (Table 6). The estimated world capacity up to 1990 is shown in Table 7.

Table 6. Production of vanadium by major producers[a,b,c]

Country	1981	1982	1983	1984
Australia	0.1	0	0	0
China, Peoples Republic of	4.5	4.5	4.5	1.8
Finland	5.2	4.8	5.0	4.5
Japan	0.7	0.7	0.8	0.9
Norway	0.9	0.4	0	0
USA	13.9	10.1	3.6	5.9
South Africa	21.0	19.6	14.5	20.4

[a] From: Wentzel (1985).
[b] Production in millions of kg V_2O_5 equivalent.
[c] Data on production in the USSR are lacking. It is probably about 10 000-15 000 tonnes.

Table 7. World vanadium capacity[a,b]

Country	1981	1982	1983	1984	1985	1990
Australia/New Zealand	0.4	1.6	0	0	0	3.6
China, People's Republic of	5.4	5.4	5.4	5.4	5.4	5.4
Finland	5.2	5.2	5.2	5.2	3.1	0
Japan	1.3	1.3	1.3	1.3	1.3	1.3
Norway	0.9	0.9	0	0	0	0

South Africa	28.4	28.4	27.2	27.2	27.2	29.5
USA	13.9	16.4	14.3	14.3	9.5	15.4
Venezuela	0	0	0	0	0	2.7

[a] From: Wentzel (1985).
[b] Capacity in millions of kg V_2O_5 equivalent.

The major producers of vanadium are China, Finland, South Africa, the USA, and the USSR.

European countries, together with Japan and the USA, use 85% of the total output.

3.2.1.1 Extraction from ores

The production of vanadium is closely linked with that of other metals (particularly iron, but also uranium, titanium, and aluminium). It is sometimes extracted from ores directly as a vanadium-rich alloy (e.g., ferrovanadium).

3.2.1.2 Extraction from fossil fuels

Petroleum is a source of vanadium. A number of oilfields have a high vanadium content; the vanadium level in vanadium-rich oil ash amounts to as much as 600 - 700 g/kg (Holodov, 1968; Borisenko, 1973; Aleshin et al., 1974; NAS, 1974). For this reason, vanadium is extracted from petroleum ash in some of countries (e.g., Canada, Italy, USA).

All coals contain vanadium, concentrations in various coalfields ranging from extremely low to 10 g/kg (in coal) (e.g., Argentina, USSR) (Holodov, 1968, 1973; Borisenko, 1973; NAS, 1974). Coal ash constitutes a supplementary source of vanadium (up to 300 g/kg).

Tar sands (Canada), bitumens, and asphaltites (Argentina, Peru, USA, USSR) are potential sources of vanadium. For instance, burning bitumen from the Sadkinskoe deposit (USSR) yielded an ash containing 43 - 66% vanadium pentoxide (Holodov, 1968, 1973).

3.2.1.3 Extraction from slag

In some countries, vanadium is extracted from slag resulting from the metallurgical production of catalysts (Pilz & Komischke, 1972; Rose, 1973) or the processing of vanadium catalysts. The levels of vanadium pentoxide in slags obtained from Bessemer converters of pig iron made from Kachkanar ores (USSR) were 135 - 140 g/kg (Pastuhov & Tretjakov, 1959). Slag obtained at a factory in South Africa contained a vanadium pentoxide concentration of about 250 g/kg (NAS, 1974).

3.3 Consumption and Use

3.3.1 Metallurgy

Vanadium has important industrial uses, mainly in ferrous metallurgy, where 75 - 85% of all vanadium produced is used as an alloy additive in making special steels. Pure vanadium is very seldom used as it reacts easily with oxygen, nitrogen, and

carbon at a relatively low temperature (300 °C).

To produce various high-resistance carbon steels, vanadium is combined with chromium, nickel, manganese, boron, tungsten, and other elements. The amount of vanadium in the steel ranges from 0.3 to 51 g/kg (Goldshtejn, 1967; Grin et al., 1971). Vanadium may be a component of structural steels used in building, transport, engineering, and boiler-making and in tool steels. It is added to steel in the form of either ferrovanadium (an iron/vanadium alloy containing 400 - 800 g vanadium/kg) or vanadium carbide. Vanadium is also a major alloying element in high-strength titanium alloys. The amounts of vanadium used in recent years in the ferrous metal industries of four major consumer countries are listed Table 8.

Table 8. Use of vanadium in ferrous metallurgy (tonnes)[a]

	1964	1965	1966	1967	1968	1969	1970	1971	1972
Canada	115	113	-	-	-	187	231	-	-
France	209	239	225	340	342	539	518	402	409
United Kingdom	600	600	600	500	600	800	800	600	500
USA	-	3709	4180	3425	3997	4333	3667	3346	-

[a] From: US Bureau of Mines (1974).

3.3.2 Other industries

The consumption of vanadium by branches of industry other than metallurgy has increased, as can be seen from the values given for the USA in Table 9.

Table 9. Use of vanadium in non-ferrous USA industries (tonnes)[a]

1965	1966	1967	1968	1969	1970	1971
562	703	1325	988	1250	991	810

[a] From: US Bureau of Mines (1974).

Alloys of vanadium with non-ferrous metals (aluminium, titanium, copper, etc.) are widely used in the atomic energy industry, aircraft construction, and space technology. Vanadium disilicide is used in the production of high-temperature refractory products (Kubasky, 1957). With regard to the production of chemicals, vanadium oxides and vanadates have important applications as catalysts in: the synthesis of sulfuric acid; the oxidation of organic compounds; petroleum cracking; purifying exhaust gases; and oxidizing ethanol. These vanadium compounds are also used in producing glass of different types and colours, organic ion exchangers, luminescent compounds, ethylene-propylene synthetic rubber, thermistors, and switching elements. The pentoxide and various other salts of vanadium are used in preparing glazes and enamels for porcelain and pottery, in producing lacquers and paints, and as developers, sensitizers, and colouring agents in photography and

cinematography. Vanadium is also used as a mordant in the dyeing and printing of cotton, particularly for fixing aniline black on silk. Europium-activated yttrium vanadate is used in colour television tubes. Vanadium hydride can be used as a neutron moderator in atomic reactors. Soluble salts of arsenous-vanadous acid have been used as fungicides and insecticides. Vanadium slags are used in casting shops as a moulding material to improve the quality of the casting surface and to facilitate cleaning.

In most of these applications, the quantities of vanadium used are small. Some recycling takes place (e.g., with catalysts).

3.4 Environmental Pollution Resulting from Production, Use, and Waste Disposal

Fig. 1 shows the cycle of the various chemical processes involved in the production and recovery of vanadium. Expansion of the mining and processing of vanadiferrous materials, and of the use of vanadium in metallurgical and other industries, and the use of petroleum at power stations and in engineering, can lead to increased pollution of the atmosphere and watercourses with vanadium compounds. Pollution is mainly by the penta- and trivalent oxides.

3.4.1 Metallurgy

The most important industry with respect to vanadium pollution is the metallurgical industry, in which vanadium is used to obtain steel alloys. Because of the relatively low melting point of vanadium pentoxide (690 °C), its fumes may enter the air, condense, and form an aerosol with particle diameters of up to 2 μm (Roshchin, 1968). Obviously, these processes may lead not only to contamination of the air in industrial premises, but also to contamination of the outdoor atmosphere (where an aerosol of vanadium pentoxide forms part of the smoke emission). Vanadium pentoxide was found in 87% of all air samples taken in the vicinity of large metallurgical plants, in concentrations ranging from 0.98 to 1.49 $\mu g/m^3$. Concentrations in 11% of the samples exceeded 2 $\mu g/m^3$ (Pazhynich, 1967).

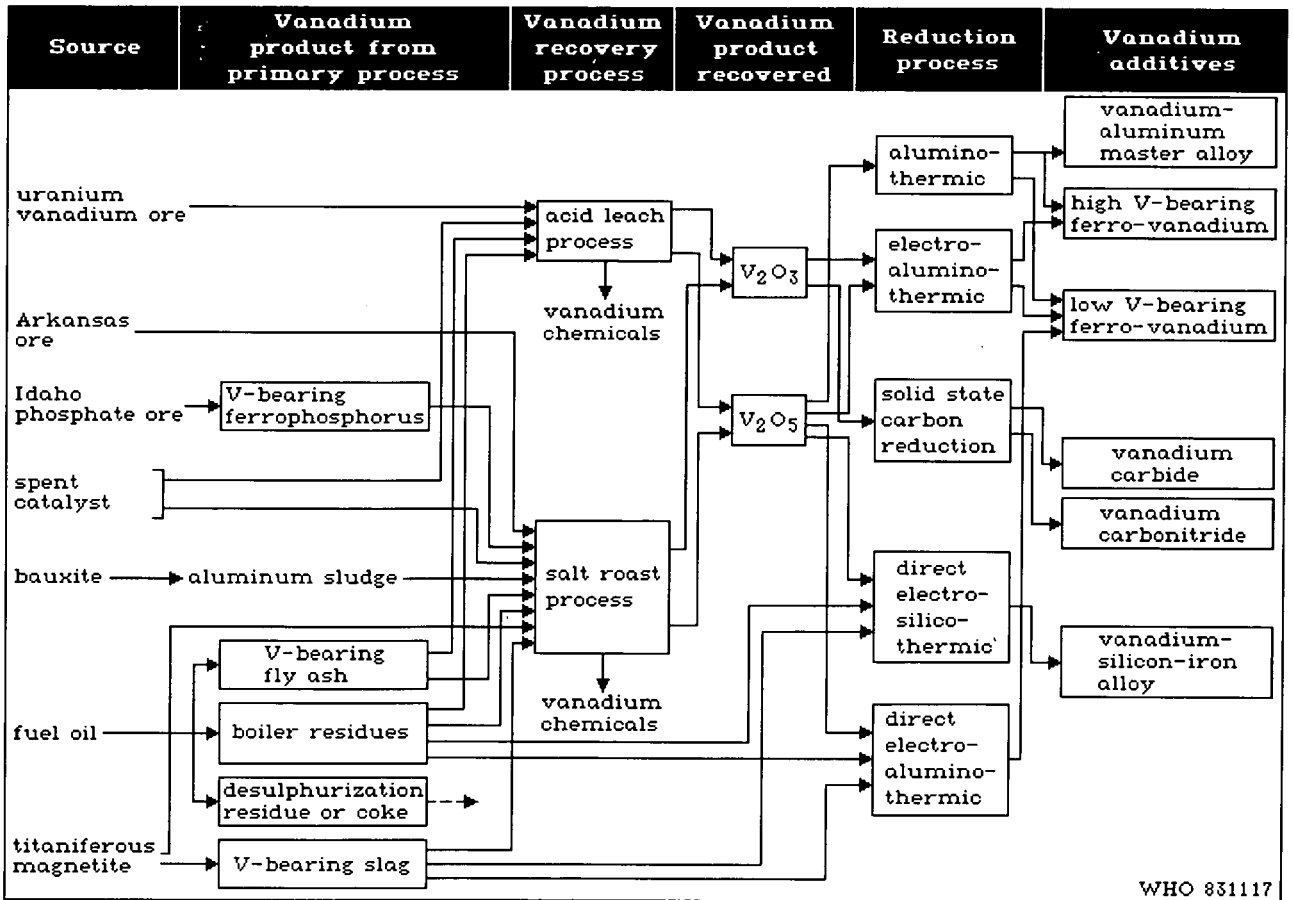
The process of re-smelting steel scrap also leads to the discharge of a vanadium-containing aerosol into the atmosphere. In 1968, in the USA, 43.5 million tonnes of steel were produced from the re-smelting of scrap in basic oxygen furnaces. The emission factor was calculated to be 21 kg particulates per tonne of steel produced and the degree of emission control 97%. The aerosol discharged into the air during this process contained a vanadium concentration of 0.02%. Based on these figures, an estimated 6 tonnes of vanadium escaped into the atmosphere (US EPA, 1977).

Ferrovanadium used for alloys in steelmaking is produced in electric arc furnaces. The charge consists of scrap steel, fused sodium metavanadate, and carbon with silicon, aluminium, or a combination of the last two elements, as a reducing agent. An estimated 131 tonnes of vanadium were discharged into the air as a result of ferrovanadium production in the USA in 1968 (US EPA, 1977).

Discharge into the atmosphere is greatest from furnaces roasting vanadium slags, vanadium pentoxide smelting furnaces, electric furnaces, crucibles in which ferrovanadium is melted, and crushing equipment (US EPA, 1977).

Metallurgical slag may contain significant concentrations of vanadium. When titaniferrous and vanadic magnetite iron ores are converted into steel, the resulting slag contains vanadium pentoxide concentrations of up to 250 g/kg (Dovgopol et al., 1974; NAS, 1974). Vanadium is released into the atmosphere during the loading, transporting, unloading, and crushing of slag. The slag formed when iron is smelted contains considerably less vanadium than converter slag. However, in view of the considerable and increasing use of blast-furnace slags as building-materials and in motorway construction, they can be sources of environmental pollution. For example, in a plant smelting vanadium-containing titaniferrous magnetite, the losses of vanadium in slag represented 18% of the vanadium content of the original raw material (Dovgopol et al., 1974).

The solid wastes formed as a result of roasting slag during the production of technical vanadium pentoxide may be another source of environmental pollution. In this process, an average of 5.16 tonnes of solid waste containing 1.2% vanadium pentoxide are formed for every tonne of vanadium pentoxide produced (Kurmaev, 1974).



Generalized flowsheet: minerals that are processed to form vanadium products
From: NAS (1978).

The liquid waste and wash water from metallurgical plants often contain large amounts of vanadium, up to several hundred milligrams per litre, measured as vanadium pentoxide. Kurmaev (1974) detected vanadium at a level of 702.8 mg/litre in effluent from a vanadium pentoxide plant. In a new ferrovanadium plant, purified waste water contained 340 mg vanadium pentoxide/litre (Kurmaev, 1974). Unpurified waste-water discharge from a vanadium pentoxide plant into an open watercourse produced a vanadium level in the watercourse of 2 mg/litre (Seljankina, 1961). Linstedt & Kruger (1969) found the highest river concentrations of vanadium near uranium-vanadium plants and the lowest in water samples taken upstream from the industrial areas (Table 2) (section 3.1.3). In studies by Shilina & Malakhov (1974), water samples taken from the Moscow River below the city contained 6 times as much vanadium as samples taken above the city (0.06 and 0.01 mg/litre, respectively).

The pickling of steel casts or steel articles can include vanadium in the pickling mixture. Waste hydrochloric, nitric, hydrofluoric, and sulfuric acids from a steel smelting plant contained 0.02% vanadium. The solid residue on the bottom of the acid vats contained 2.4 g vanadium/kg (hydrochloric acid vat) and 1.6 g vanadium/kg (nitric and hydrofluoric acid vats) (Kurmaev, 1974); vanadium in waste acid that is not properly treated may be a source of water pollution.

3.4.2 Fossil fuel combustion

Industrial plants producing power and heat and operating on petroleum, coal, and heavy oils are the most widespread source of vanadium discharge into the environment. In 1969, as a result of the combustion of fossil fuels (coal and oil), about 20 000 tonnes of vanadium were discharged into the air in the USA (NAS, 1974). The estimated levels of emission from burning coal in the USA for 1969 are shown in Table 10.

In a study of the vanadium discharged from coal burning in six electric power generating stations, the total amount discharged into the air in 1968 was 3760 tonnes. Where there were no ash-trapping devices, 65% of the ash entered the atmosphere. The degree of atmospheric dispersion of ash particles depended on the original coalfield, the size of coal used, the type of furnace, the combustion conditions, and the presence and type of ash-trapping devices (NAS, 1974).

In a study of the metal aerosol content of waste gas emissions from an oil-fired electric power station, it was reported that the concentration of vanadium pentoxide (and oxides of aluminium, chromium, iron, and manganese) was not affected by the type of boiler or mode of operation. Comparison of the metal content in the fuel oil and waste gases showed that 90% was released into the atmosphere (Sokolov, 1986). In the USSR, there is a trend towards a reduction in the use of heavy fuel oils in electric power stations.

Other possible sources of vanadium discharge into the air

are the burning of coal tips or dumps of coal dust in mining areas, but data are not available.

All crude petroleum oils contain vanadium at levels ranging from 1 to 400 g/tonne, depending on the oilfield (Holodov, 1968, 1973; Shah et al., 1970; Christian & Robinson, 1971; Nelson, 1973; NAS, 1974). In the distillation of crude oil, almost all the vanadium remains in the high relative molecular mass hydrocarbon fractions. The vanadium contents of heavy fuel oils range widely from 1 to 200 g/tonne and are almost a thousand times greater than those of petroleum distillates. Assuming that 10% of the vanadium is precipitated inside the plant (flue and ash trap) while 90% is discharged into the air, it has been calculated that atmospheric emissions in the USA as a result of heavy fuel oil combustion were about 14 100 - 21 800 tonnes in 1970 (Holodov, 1968, 1973; NAS, 1974). Similar percentages were found by Sokolov (1986).

Table 10. Estimated emissions of vanadium resulting from coal burning in the USA, 1969[a]

Type and use of coal	Coal (1000 tonnes)	Vanadium in coal (tonnes)	Vanadium in fly ash (tonnes)	Control of fly ash (%)	Vanadium discharged into the air (tonnes)
Bituminous coal					
Electric power utilities	308 642	9254	6015	85	902
Manufacturing	93 248	2797	1818	60	727
Retail deliveries	12 665	380	247	50	124
Coking	92 901	2787	-	100	0
Subtotal	507 276	15 218	8080		1753
Anthracite coal	9275	1159	753	50	377
Total					2130

[a] From: NAS (1974).

Distilled petroleum fuels produced in the USA (gasoline, kerosene, diesel fuel, home-heating oils) contain 0.05 mg vanadium/kg (NAS, 1974). The distillation process used leaves nearly all of the vanadium originally present in the residual fractions. Analyses of the spent gases from petrol engines, sampled directly at the exhaust outlet, showed vanadium concentrations of 0.1 - 0.2 mg/kg, and exhaust gases of diesel engines contained 10 - 15 mg vanadium/kg. Six to 12 mg/kg of vanadium was found in soot collected from the edges of flues in a small oil-fired power station (Pilz & Komischke, 1972).

The amount of vanadium in natural gas is less than

0.5 g/tonne, and almost no vanadium is released into the atmosphere on combustion (NAS, 1974).

3.4.3 Agriculture

Vanadium has been used as a trace fertilizer applied at the rate of 0.75 - 1 mg/kg soil (Peterburgskij & Tormasova, 1969). This practice must lead to an increased level of vanadium in the soil, but further information on agricultural use is not available.

3.5 Transport and Transformation

3.5.1 Geochemical processes

Vanadium is involved in various geochemical processes occurring in the earth's crust. There is extremely wide dispersion of vanadium during the formation of volcanic rocks and sporadic accumulation with the formation of vanadium minerals as a result of postmagmatic processes. Like all trace elements that accumulate in soils, vanadium migrates within the soil itself and within the system: rock-water-soil-vegetation-animals-man.

During geochemical processes in the soil and in weathering and podzolization, vanadium is shifted from the A horizon to the B horizon (Kovda et al., 1959). However, vanadium shifting does not occur during weathering processes that do not involve movement of sesquioxides.

Vanadium concentrations in rocks are linked to the pH of the rocks (Borisenko, 1973). Neutral and acid rocks contain lower vanadium concentrations than basic rocks, and acid rocks contain lower concentrations than neutral rocks. In magma of various types (the main carrier of vanadium), about 92% of all vanadium occurs in basic rocks (basalts, gabbro, amphibolites, and eclogites), and about 8% occurs in acid and neutral rocks. Less than 1% of the total amount of vanadium is found in ultrabasic alkaline rocks.

The main carriers of vanadium in the sedimentation process are ferric hydroxides and solid bitumens. The great affinity between the crystallochemical properties of V^{3+} and Fe^{3+} is of vital importance for the diffusion of vanadium. There is roughly 400 - 500 times more iron than vanadium in the earth's crust. Thus, iron is a "solvent" of trivalent vanadium, and is responsible for its diffusion in magmatic rocks. The bulk of the ferromagnesian rock-forming minerals (and also titaniferrous magnetite and magnetite itself) trap vanadium during the crystallization of rocks, and, during endogenous processes, vanadium is very closely linked with trivalent iron. In the formation of igneous rocks, vanadium is preferentially concentrated in those with a high iron content.

3.5.2 Biogeochemical processes

The accumulation of vanadium in soils and in all other materials depends directly on its concentration in the soil-forming rocks, the atmosphere, and the oceans of the world.

Migration, diffusion, and concentration of vanadium in the biosphere takes place as a result of its extraction by living organisms from water, from food of both vegetable and animal origin, and from different types of rock during their decomposition and the formation of soils.

3.5.2.1 Transport in, and removal from, water

In assessing the relative importance of the two ways in which vanadium is transported in water, Konovalov et al. (1968) and Holodov (1968) concluded that 87% is carried away by the rivers in suspended form, and 13% in solution. The average level of dissolved vanadium in the rivers of Japan and the USA (Sugawara et al., 1956; Durum & Haffty, 1963) were the same as that recorded by Konovalov et al. (1968), i.e., 0.001 mg/litre.

The bulk of vanadium enters sea-water in suspended form or sorbed on colloids. It accumulates in recent deposits, passes through watercourses mechanically, and does not react chemically with sea-water. This peculiarity of vanadium transport is reflected in its distribution on the sea-bed in the form of silt.

The fate of vanadium that is dissolved in water is more complex. As very large amounts of dissolved vanadium have been carried out into the oceans throughout all geological periods, vanadium levels in sea-water of about 60 mg/litre might be expected; in fact, levels do not exceed 0.003 mg/litre (Goldschmidt, 1938; NAS, 1974), indicating that vanadium is continuously removed from sea-water. Krauskopf (1963) concluded that the vanadium content of sea-water is not dependent on solubility and that natural reagents remove vanadium from the water. There are two possible pathways, namely sorption and biochemical processes. The migratory qualities of vanadium are poor. The content of vanadium in the earth's crust is 0.015 g/kg (Vinogradov, 1959), and a mean content in river water is 0.001 mg/litre. Thus, very little vanadium is transported via water. The bulk of vanadium is precipitated on to the seabed and becomes bound to silts (Petkevich et al. 1967; Strahov, 1968). Levels of vanadium dissolved in sea-water amount to 0.001 - 0.003 mg/litre. The vanadium comes from the 10% dissolved in river water and is continuously precipitated from the water by ferric hydroxides and organic matter (Krauskopf, 1963).

Biochemical reactions play an important role in the extraction of vanadium from sea-water and conversion into a sediment (Vinogradov, 1937; Holodov, 1973). This is confirmed by the link between the concentrations of vanadium and organic substances in sedimentary rocks and silt. However, in practice, it is extremely difficult to determine the part of the vanadium that has been assimilated by organisms and the part that has been sorbed by the decomposing mass of organic matter or introduced in dissolved form.

An important role in the biogenic migration of vanadium is played by live marine organisms and plants. The ascidians and holothurians are noteworthy vanadium accumulators (Bertrand, 1950) (section 3.1.6). Some marine algae are also capable of accumulating vanadium (Krauskopf 1963). When they die, these

organisms promote accumulation of vanadium in the silt.

Thus, vanadium dissolved in sea-water is continuously removed either by sorption or biochemical processes. In the first case, the main precipitant is hydrated ferric trioxide; in the second, vanadium is accumulated by marine animals, plankton, and, less commonly, algal and plant organic material.

3.5.2.2 Occurrence in hydrocarbons

The accumulation of vanadium in organic concentrators is linked with its occurrence in hydrocarbons (petroleum, asphalts, peats, bitumens, and coal). Vanadium may enter petroleum together with organic matter or accumulate in already-formed petroleum from underground waters and petroliferous strata. Apparently, both processes occur in nature. Secondary transformation of petroleum into asphalt is accompanied by a proportionate increase in the concentrations of the tar-asphalt component and the vanadium linked to it (Vernadskij, 1940).

3.5.2.3 Biospheric redox processes

Vanadium takes part in redox processes not only of a geochemical nature but also in plants and animals. Pejve & Ajzupiet (1974), studying the intracellular distribution of metals in plants, showed that a considerable number, including vanadium, were linked to complex lipid substances of comparatively high stability that persisted, even after the cells had died. These lipids persisted in soils and silts and served as a source of metal in sedimentary rocks. In various types of plants, the proportional relationship between the level of iron and those of manganese, copper, titanium, nickel, chromium, cobalt, and vanadium decreased in the course of evolution, and was least significant in the leaves of flowering plants.

In a number of soil organisms, such as *Micrococcus lactolyticus*, Thiobacillus terrooxidans, and *Ferrobacillus thiooxidans*, there was a link between iron and vanadium in biochemical processes (Zajic, 1969).

3.5.2.4 Transport in air

Information on the local movement and deposition of airborne vanadium is presented in section 4.1.1. Strahov (1947) and Ronov (1964) concluded that the gaseous envelope of the earth is not of significant importance in the transport of vanadium, but a study by Duce & Hoffman (1976) documented some transport of man-made airborne vanadium over ocean areas. The authors estimated that about 10% of this material was deposited in the ocean. In a study of trace metals in European glaciers, Jaworowski et al. (1973) showed the presence of small amounts of vanadium, apparently deposited from the air, which had increased in recent decades.

4. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

4.1 General Population Exposure

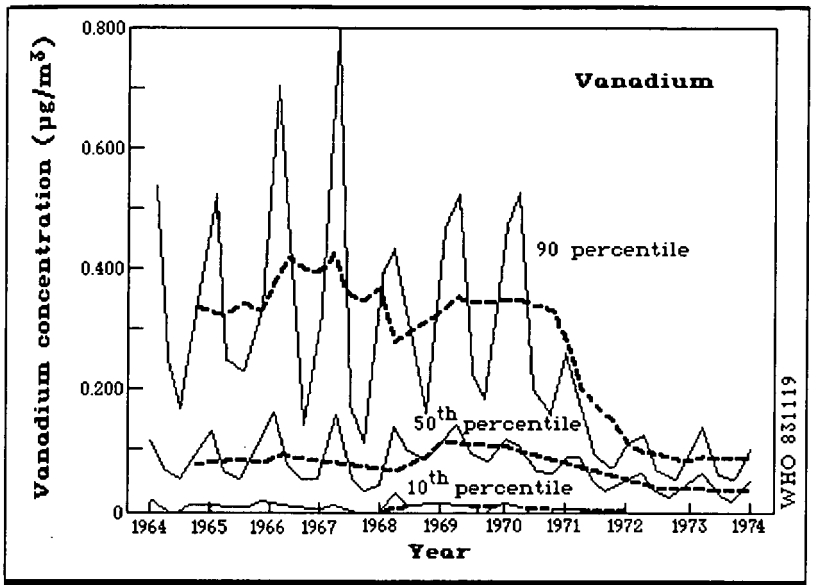
4.1.1 Air

Natural sources of vanadium, such as continental dust and marine aerosols, cause only low natural background levels of vanadium in air. In remote areas, such as the South Pole, the concentrations range from 0.001 to 0.002 ng/m^3 (Zoller et al., 1974), and in the eastern Pacific Ocean, from 0.02 to 0.8 ng/m^3 (Hoffman et al., 1969). In rural areas in Canada, the United Kingdom, and the USA, concentrations have been reported to range from 0.2 to about 75 ng/m^3, with annual averages frequently below 1 ng/m^3 (Rahm, 1971; Cawse & Peirson, 1972; US EPA, 1977). In general, air levels of vanadium are higher in urban areas than rural areas. Annual averages may often be in the range of 20 - 100 ng/m^3, though, exceptionally, higher averages exceeding 200 - 300 ng/m^3 have been recorded in large cities, and the maximum 24-h average may exceed 1000 ng/m^3 (US EPA, 1977). In all surveys, there have been conspicuous geographical and seasonal variations. High concentrations of vanadium in air have been attributed to the local burning of fuel oil with a high vanadium content. The uptake of vanadium fall-out by mosses *(Hypnum capressiforme and Bryum argenteum)* in the Stockholm area indicates that heating oil is a major source of vanadium (Rühling, 1971). In this regard, Faoro & McMullen (1977) presented some interesting data (Fig. 2). The values shown, especially for the period prior to 1971, are typical of cold-climate cities where high-vanadium heavy fuel oils are extensively used. The marked seasonal variations are due to alterations in heating requirements and seasonal differences in atmospheric inversions. The marked decline after 1970 is due to the introduction of low-sulfur fuels; reduction of sulfur in oil results in a proportional reduction in the vanadium content. A similar effect can be produced by changing from heavy to distilled fuel oil, as noted in Boston by Barry et al. (1975), where levels of airborne vanadium for comparable months in 1966 and 1972 were 1.07 and 0.114 μg/m^3, respectively.

These data illustrate the importance of fossil fuels as sources of vanadium in urban air. The patterns observed in other areas are similar but less extreme in concentration and fluctuation. Because of the variations in vanadium concentrations in oil and coal, community levels will depend mainly on the actual vanadium concentrations in the fuels used and on meteorological factors.

Pollution of the air by industrial facilities may be less than that by power stations and heating equipment. At a steel plant in the USA in 1967, concentrations of vanadium ranged from 0.04 to 0.107 μg/m^3 and averaged 0.072 μg/m^3, corresponding to the mean concentration over 13 Pennsylvania towns (also 0.072 μg/m^3) (NAS, 1974). The following levels of vanadium pentoxide were found by Pazhynich (1967) in the USSR in areas of extensive metallurgical activity not connected with vanadium production: in the years 1964-65: 1.49 μg/m^3 at 150 m from the source of discharge; 0.47 μg/m^3 at 500 m; 1.35 μg/m^3 at 1000 m; and 0.98 μg/m^3 at 1500 m. Near a plant producing technical vanadium pentoxide, Kurmaev (1974) detected the following 24-h mean levels of vanadium pentoxide: 0.004 - 0.012 mg/m^3 at 500 m from the source; 0.001 - 0.006 mg/m^3 at 1000 m; and 0.001 - 0.004 mg/m^3 at 2000 m. Seventy to 72% of

the particles were less than 2 μg in diameter.



Seasonal variations in quarterly average levels of vanadium in air at urban sites in northeastern USA. From: Faoro & McMullen (1977).

Boyarkina et al. (1978) studied vanadium precipitation in and around an industrial city, in winter, by measuring concentrations in snow. In the central area, a concentration of 24 μg/litre was found, decreasing to 3.2 μg/litre at a distance of 40 - 50 km.

4.1.2 Water

Natural background levels of vanadium in water have been discussed in section 3.1.3, and levels in industrial effluent, in section 3.4.1. Durfor & Becker (1963) included vanadium in their analyses for trace elements in drinking-water supplies in large cities in the USA. Of the samples analysed, 91% showed less than 10 μg vanadium/litre; the maximum concentration was 70 μg/litre, and the average was about 4.3 μg/litre. Many of the samples were negative. Twenty-six percent of 3676 tap water samples from 34 areas in the USA contained vanadium at concentrations ranging from 1.3 to 33 μg/litre with a mean of 4.85 μg/litre (Greathouse & Craun, 1979).

Hoffmann et al. (1972) published data from a regional well-water survey in Poland. The average vanadium concentrations were 0.06 - 6 μg/litre, with a maximum single value of 15 μg/litre. Bottled waters from mineral springs frequently contained higher levels; Schlettwein-Gzell & Mommsen-Straub (1973) reported a range of 4 - 290 μg/litre in bottled waters from Switzerland.

Highly-mineralized waters in Argentina contained 0.3 - 10 μg vanadium/litre (Trelles et al., 1970). These concentrations often occur in conjunction with high concentrations of arsenic and/or fluorides.

4.1.3 Food

4.1.3.1 Individual foods

Information on the vanadium contents of human food is sparse. Data from two studies (Myron et al., 1977; Byrne & Kosta, 1978) are combined in Table 11 with those from an earlier study using a similar method (Söremark, 1967). The results of these studies agree reasonably well, but differ in some respects from the results of earlier work, especially that of Schroeder et al. (1963). The principal difference is that Schroeder noted high vanadium concentrations in fats and oils, whereas low concentrations were found in the more recent studies. Such a difference may be accounted for by the use of different analytical methods. Similar discrepancies have been encountered in the study of other trace elements, i.e., lower concentrations have been found using more recently developed methods.

The data presented in Table 11 show low levels of vanadium in most elements of the human diet. There are also some interesting differences among specific foods. Grains contain higher levels of vanadium than fruits and vegetables. Levels in oils and fats and beef and pork are low, but those in the liver and kidneys of cows and pigs are higher. Higher levels are found in both the flesh and internal organs of the chicken, and levels in fish flesh are also high. Vanadium levels in milk and eggs are low, and those in beer and wine are high. Myron et al. (1977) pointed out that processing appears to raise levels in food (e.g., white versus brown rice; cereal, flour, bread, and gluten versus grain; peanut butter; bologna and bacon versus pork). No explanation was given for the very high levels in dill and parsley.

Table 11. Vanadium concentrations in foods (μg/kg)[a]

	Study 1	Study 2	Study 3
Grains			
Wheat		3.6	
Flour			15, 40
Bread		11.20	10, 13
Gluten		33	
Oats			3
Oatmeal		6	
Corn			0.7
Cornmeal		2	
Brown rice		1	
White rice		21	12, 30
Barley		14	1.6
Cereal		93	
Fruits			
Apple	1.1	4	0.3
Pear	0		0.2
Banana		3	0.2
Orange			1
Cherry			0.4
Apricot			0.2
Peach			0.2
Strawberry	31.41 (dry)		
Blueberry	1.6		
Vegetables			

Potato	0.8	1	1.2, 1.9
Radish	52	5	0.6
Carrot	0	1	2.3, 2.4
Beet	0		
Garlic			0.6
Onion			0.6
Leek			0.3
Navy bean		14	
Pea	0	7	0.4
Tomato	0.03	2	0.3
Cucumber	2.1		
Squash		4	
Brussels sprout			0.5
Cauliflower	0.08	1	0.9
Cabbage		2	0.3
Lettuce	21	4	1.0, 2.7

Table 11 (contd).

	Study 1	Study 2	Study 3
Spinach			35
Parsley	790		1800 (dry)
Mushroom			50 - 2 000 (dry)
Dill	140	431	
Meats			
Beef	0	1	0.4 - 1.3
Beef liver	2.4, 10	6	7.3
Pork	0	1	0.6, 0.9
Pork liver			8.4
Pork kidney			8.5
Bacon		5	
Bolgna		8	
Chicken, white		22	1.7
Chicken, dark		12	
Chicken liver			37, 38
Chicken kidney			18
Cod		28	7.2
Mackerel	2.6		3.5
Tuna		11	10, 3
Lobster	43	5	
Scallop		22	
Oils and fats			
Margarine		4	
Soybean oil		1	
Corn oil		1	3
Pumpkin seed oil			0.2
Lard		2	0.2
Nuts			
Hazel nut			3.7
Peanut butter		44	
Dairy products			
Milk	0 - 0.1	3	0.2, 0.2
Powdered milk	0 - 0.2	25	
Chocolate milk		21	
Butter		1	

Egg white		0.3 - 1.8
Egg yolk		2.0 - 3.6
Beverages		
Coffee	1.6	
Tea	1.3	0.3
Cola	0.7	1.5
Beer	11	8.4
Wine		3.5 - 3.2

[a] Study 1: Söremark (1967) (neutron activation analysis).
Study 2: Myron et al. (1977) (atomic absorption spectroscopy).
Study 3: Byrne & Kosta (1978) (neutron activation analysis).

4.1.3.2 Complete diets

Byrne & Kosta (1978) estimated the daily intake of vanadium to be "a few tens of micrograms," but added that it may vary considerably. Assuming a very low rate of intestinal absorption of vanadium in man (section 5.1.2), Byrne & Kosta calculated intakes for 3 adults in whom they measured dietary concentrations. The calculated intakes were 36, 66, and 11 µg/day, respectively.

Analyses of 9 selected hospital diets (Myron et al., 1978) are given in Table 12. Each meal was prepared and analysed separately by atomic absorption spectroscopy. The results were similar to concentrations found in individual foodstuffs in other studies given above. In a later study, Byrne & Kosta (1979) reported on the determination of vanadium in total diet samples obtained during a nutrition survey in 5 Italian towns (Table 13). The concentrations agree with those reported by Myron et al. (1978).

Table 12. Daily vanadium intake in diet[a]

Diet type	(µg/day)	(µg/g)	(µg/1000 cal)
General-1	13.6	0.019	4.7
Cholesterol reducing-1	25.6	0.034	8.8
Cholesterol reducing-2	16.8	0.022	5.8
Cholesterol raising	30.1	0.046	10.5
General-2	28.0	0.040	9.8
Low calorie	12.4	0.029	10.6
Low salt	15.5	0.028	9.1
Puree	26.0	0.050	14.1
Soft	15.8	0.024	6.4

[a] Adapted from: Myron et al. (1978).

4.2 Occupational Exposure

In terms of occupational exposure, the most important vanadium compounds are vanadium pentoxide, vanadium trioxide, ferrovanadium, vanadium carbide, and vanadium salts, such as sodium and ammonium vanadate. The oxides and salts are commonly used in industry in powder form, giving rise to the possibility of dust and aerosol formation, when the substances are crushed or ground. Many metallurgical processes involve the production of vapour containing vanadium pentoxide, which condenses to form respirable aerosols. Boiler-cleaning operations generate dusts containing the pentoxide and trioxide compounds. Combustion of residual fuels with a high vanadium content is likely to produce aerosols of the pentoxide as well as oxide complexes of vanadium with other metals.

Table 13. Vanadium contents of Italian freeze-dried total diet samples[a]

Town	Dry weight (g)	Vanadium concentration[b] (ng/g)		Daily vanadium intake (μg)	
Aosta	310	32.1	0.9 (2)	10.0	
L'Aquila	173	46.0	3.4 (2)	8.0	
Montfalcone	278	39.7	4.1 (2)	11.0	
Mt. Amiata	377	29.7	0.8 (2)	11.2	
Rome	285	42.3	4.6 (4)	12.0	
Mean values		38.0	6.9	10.4	1.5

[a] From: Byrne & Kosta (1979).
[b] Average and standard deviation; number of aliquots in parentheses.

4.2.1 Metallurgy

The processing of metals containing vanadium includes chemical treatment and high-temperature operations. However, only moderate concentrations of vanadium were found in the breathing zone of workers engaged in operations that would be expected to produce the greatest fume exposure. During the addition of vanadium to furnaces, concentrations ranged from 0.006 to 0.08 mg/m^3 and, during tapping, from 0.004 to 0.02 mg/m^3. Concentrations found in oxyacetylene cutting ranged from 0.008 to 0.015 mg/m^3 and, in arc-welding, from 0.002 to 0.006 mg/m^3 (NAS, 1974).

Vanadium levels in metallurgical plants have been studied in detail (Roshchin, 1968). Vanadium slag contains about 11 - 13%, mainly in the form of trioxides of vanadium (measured as vanadium pentoxide). Slags are used for the production of vanadium pentoxide and ferrovanadium, and the process is accompanied by extensive formation of iron oxide aerosol. Air

concentrations of the dust (mainly vanadium trioxide) found in the main working positions (converter operator, mixer, and crane driver) ranged from 20 to 55 mg/m^3. Measured as vanadium pentoxide, the contents of the swirling dust did not exceed 0.17 mg/m^3. About 75% of the dust particles had a diameter of less than 2 μm and 20% had a diameter of between 2 μm and 4 μm.

Breaking, loading and unloading, crushing and grinding, and magnetic separation of vanadium slag causes thick dust formation, with concentrations ranging from 30 to 120 mg/m^3. The slag contains 111 - 129 g vanadium pentoxide/kg. A diameter of less than 2 μm was recorded for 70 - 72% of the particles; 86 - 96% had a diameter of less than 5 μm. When the slag is roasted, free vanadium pentoxide is discharged into the work-place air; atmospheric concentrations in the vicinity of furnaces ranged from 0.04 to 1.56 mg/m^3. During leaching and precipitation, concentrations of vanadium in the air may be high, sometimes exceeding 0.5 mg/m^3.

The smelting and granulation of technical vanadium pentoxide are accompanied by the formation of an aerosol. This aerosol escapes when the product is poured for granulation. During the loading of smelting furnaces, concentrations of vanadium pentoxide ranged from 0.15 to 0.80 mg/m^3. During smelting and granulation, concentrations ranged from 0.7 to 11.7 mg/m^3. In other parts of the work-place, concentrations may range from 0.03 to 0.2 mg/m^3.

In aluminium production, when bauxite is being converted into alumina, the aluminate solutions accumulate vanadium salts, which crystallize and precipitate out. Precipitated sodium polyvanadate is smelted to form vanadium pentoxide, which is cooled and settles in the form of thin plates. Vanadium pentoxide dust (concentrations of up to 2.3 mg/m^3) is given off only in the terminal phase during tapping of the liquid product, packing, and loading.

During the drying, sieving, and calcination of ammonium vanadate and during the crushing, unloading, and packaging of pure vanadium pentoxide, dusts are formed. When vanadium pentoxide is sieved after calcination, the concentration in air may range from 2.2 to 26 mg/m^3. In plants with less mechanization, incomplete sealing of equipment, and inefficient local exhaust ventilation, concentrations of dust during these operations ranged from 4.9 to 48.9 mg/m^3.

In the production of ferrovanadium, there is a continuous source of discharge of vanadium pentoxide and lower oxides during the smelting process. Data on vanadium in air at various sites are shown in Table 14.

Using spectrophotometric techniques, Roshchin (1968), Katayeva & Sapunov (1974) and Kazimov (1977) found high concentrations of vanadium during smelting and granulation (range, 0.16 - 1.89 mg/m^3; mean, 0.59 mg/m^3; 104 samples), production of ferrovanadium (range, 0.58 - 4.81 mg/m^3; mean, 1.7 mg/m^3; 110 samples), and roasting of the charge (range, 0.44 - 3.64 mg/m^3; mean, 1.52 mg/m^3; 112 samples).

Table 14. Vanadium levels in the air of a ferrovanadium plant[a]

Work-place/operations	Vanadium pentoxide (mg/m^3)	Lower oxides of vanadium (mg/m^3)
Work area of smelters and helpers	0.1 - 2.6	0.05 - 1.2
Unloading of vanadium pentoxide from the bin and charging of electric furnace	2 - 124.6	
Crane driver's cabin during smelting	0.07 - 9.43	0.03 - 0.1
Cutting up ferrovanadium	0.97 - 12.6	
Maintenance of the furnace	7.5 - 30	

[a] From: Roshchin (1968).

Using high-volume sampling and atomic absorption analysis, Usutani et al. (1979) measured vanadium pentoxide concentrations in the air at several places in a vanadium refinery. The highest concentrations (higher than 1 mg/m^3) were detected in samples collected during the removal of the vanadium pentoxide flake. High-volume samples from other locations as well as low-volume samples obtained over 6.5-h work shifts showed lower concentrations (0.002 - 0.735 mg/m^3).

When ductile vanadium is produced by the aluminothermic process (based on the reduction of pure vanadium pentoxide with aluminium powder), the violent exothermic reaction leads to the release of a condensation aerosol of vanadium pentoxide. During preparation of the charge mixture, work-place concentrations of vanadium pentoxide ranged from 19 to 25.1 mg/m^3. When the burden was placed in crucibles inside the smelting chambers, concentrations ranged from 64 to 240 mg/m^3. During smelting, concentrations at the operators' workplaces ranged from 0.17 to 0.6 mg/m^3. Twenty to 30 min after smelting, levels declined to 0 -0.3 mg/m^3. Ninety-eight percent of the condensation aerosol particles produced had a diameter of less than 5 μm, and 82% had a diameter of less than 2 μm (Roshchin, 1968).

In the production of vanadium by the vacuum carbon thermic method, most of the pollution occurs during operations with vanadium trioxide (Roshchin, 1968). Mixing of vanadium trioxide in a closed mixer led to air concentrations in the workplace of from 0.019 to 0.58 mg/m^3. Unloading of the charge resulted in high concentrations of 14.7 - 29.4 mg/m^3. In the packing department, when the charge was sifted in a fume cupboard, concentrations in the breathing zone ranged from 0.58 to 4.7 mg/m^3. When the charge was being weighed out and packed in a fume cupboard, concentrations ranged from 3.38 to 6.76 mg/m^3.

Levels of vanadium-containing dust and vanadium pentoxide in

the air during catalyst production are shown in Table 15.

Table 15. Air contamination in vanadium catalyst production[a]

Operation	Dust (mg/m^3)			Vanadium pentoxide (mg/m^3)		
	Minimum	Maximum	Most frequent	Minimum	Maximum	Most frequent
Grinding and unloading vanadium pentoxide	5	45	7 - 9	1	7	1.5 - 3
Loading ground pentoxide into the bin	12	53	14 - 17	3.2	7.5	4 - 4.2
Sifting and packing granules of bulk contact substance	5	17.5	5 - 7	0.1	1	0.4 - 0.5

[a] From: Roshchin (1968).

4.2.2 Cleaning of oil-fired boilers

Significant occupational exposure to vanadium occurs during the cleaning of boilers in oil-fired heating and power plants and ships (Symanski, 1939; Roshchin, 1968; Kuzelova et al., 1977; Levy et al., 1984). Fuel oil combustion results in the formation of vanadium-containing dust, and large amounts of dust result from operations connected with removing ash encrustations in boiler cleaning and in cleaning the blades of gas turbines. Most of these operations are carried out by hand, and the dust in the air inside the boilers may range from 20 to 400 mg/m^3, the most common range being 50 - 100 mg/m^3, with the dust containing 5 - 17% vanadium pentoxide and from 3 to 10% of the lower vanadium oxides (Roshchin, 1968). Kuzelova et al. (1977) reported dust concentrations of 136 - 36 036 ml/m^3 in the air with vanadium concentrations ranging between 1.7 and 18.4 mg/m^3.

Williams (1952) published air sampling data on boiler-cleaning operations in the British power industry. He found concentrations of soot dust at different points ranging from 239 to 659 mg/m^3. The vanadium concentrations in the dust of the superheater chamber was 40.2 mg/m^3, while, in the combustion chamber, the concentration was 58.6 mg/m^3. Most (93.6%) of the dust particles had a diameter of between 0.15 and 1 μm.

4.2.3 Occupational exposure limits

Some national occupational exposure limits for vanadium in work-place air are shown in Table 16.

Table 16. Examples of occupational exposure limits for vanadium in various countrie

Country	Legal status	Exposure limit description	Va

Australia	Recommendation	Time-weighted average (TWA) (fume)[a]	0.
Belgium	Recommendation	Time-weighted average (TWA) (fume)	0.
Czechoslovakia	Regulatory requirement	Maximum allowable concentration (MAC)	
		- Time-weighted average (TWA)	0.
		- Ceiling value (fume)	0.
		- Ceiling value (dust)	1.
Finland	Regulatory requirement	Maximum allowable concentration (MAC)[a]	
		- Time-weighted average (TWA) (fume)[a]	0.
German Democratic Republic	Regulatory requirement	Time-weighted average (TWA) (fume)[a]	0.
		Short-term exposure limit (STEL)[a] (fume)	0.
Germany, Federal Republic of	Recommendation	8-h time-weighted average (TWA)[a]	0.
		Short-term exposure limit (STEL)[a] (30 min, 2x/shift)	2.
		8-h time-weighted average (TWA)[a] (fume)	0.
	Recommendation	Short-term exposure limit (STEL)[a] (30 min, 2x/shift) (fume)	0.
Italy	Recommendation	Time-weighted average (TWA) (fume)[a]	0.
Hungary	Regulatory requirement	Time-weighted average (TWA) (fume)[a]	0.
Netherlands	Recommendation	Time-weighted average (TWA) (fume)[a]	0.

Table 16. (contd.)

Country	Legal status	Exposure limit description	Va
Romania	Regulatory requirement	Ceiling value (fume)[a]	0.
Sweden	Regulatory requirement	Ceiling value[a]	0
Switzerland	Regulatory requirement	Time-weighted average (TWA)[a]	0.
USA	Recommendation	Time-weighted average (TWA)[a] (dust and fume)	0.
		Time-weighted average (TWA)[a] (dust)	0.
		Ceiling value (15 m)[a] (dust and fume)	0.

		Time-weighted average (TWA)[a] (fume)	0.
USSR	Regulatory requirement	Time-weighted average (TWA)[a]	0.
Yugoslavia	Regulatory requirement	Maximum allowable concentration (MAC)[a] - Time-weighted average (TWA)[a]	0.

[a] Measured as V_2O_5.

5. KINETICS AND METABOLISM

5.1 Physiological Role

5.1.1 Microorganisms

Vanadium is essential for the mould *Aspergillus niger* (Bertrand, 1942) and the green alga *Scenedesmus obliguus* (Arnon & Wessel, 1953; Arnon, 1958). It may play a role in photosynthesis in the latter. A need for vanadium has been shown by the yeast *Candida slooffii* at high temperatures (Roitman et al., 1969). The growth effects of vanadium in *Azotobacter* and other bacteria have been related to the ability of vanadium, in lieu of molybdenum, to catalyse nitrogen fixation reactions (Horner et al., 1942; Takahashi & Nason, 1957).

5.1.2 Animals

Vanadium deficiency has been reported in chicks (Hopkins & Mohr 1971a; Nielsen & Ollerich, 1973) and rats (Schwarz & Milne, 1971; Strasia, 1971), and vanadium is considered essential for these animals (Underwood, 1977; Vouk, 1979; Nechay, 1984).

Hopkins & Mohr (1974) observed reduced feather growth in chickens. They also reported impaired reproduction, due to decreased fertility, and increased perinatal mortality in rats fed a low vanadium diet (10 µg/kg) over 4 generations. A positive growth response in rats was observed by Schwarz & Milne (1971) when vanadium salts, at levels of between 50 and 500 µg/kg were added to a semi-purified diet (vanadium content unspecified) fed for 26 - 28 days.

In male Leghorn chicks fed vanadium in the diet at levels of 12.5 mg/kg and 25 mg/kg, body-weight gain was normal at 1, 2, 3, and 4 weeks of age (Kubena et al., 1986).

Slower growth, higher haematocrits, and higher levels of plasma- and bone-iron were reported by Strasia (1971) in rats fed diets containing less than 100 µg vanadium/kg compared with controls receiving diets containing 500 µg vanadium/kg, but these results were not confirmed in another study by Williams (1973). Hopkins & Mohr (1971a,b, 1974) reported that a diet containing less than 10 µg vanadium/kg decreased plasma-cholesterol levels in chicks at 28 days of age, increased plasma-cholesterol levels at 49 days of age, and increased plasma-triglyceride levels at 28 days of age. Nielsen & Ollerich (1973) found that administration of a diet containing 30 - 35 µg vanadium/kg to chicks decreased growth, increased

haematocrits and plasma-cholesterol levels, and impaired bone development.

Nielsen (1980) carried out further studies on chicks and rats, given different types of low-vanadium experimental diets, to examine the effects of vanadium deficiency. In rats, vanadium deficiency adversely affected prenatal survival, growth, physical appearance, haematocrit, plasma-cholesterol levels, and hepatic lipid and phospholipid levels. In chicks, low vanadium intake produced adverse effects on growth, feathering, haematocrit, bone development, plasma-cholesterol levels, and hepatic lipid, phospholipid, and cholesterol levels. However, consistent deficiency effects were not observed in chicks or rats in any of the studies. Nielsen (1980) suggested that the inconsistency in vanadium deficiency effects might be due to the fact that different experimental diets had different effects on the metabolism of vanadium.

Vanadate appears to have an insulin-like action (Heyliger et al., 1985). In female Wistar rats made diabetic with streptozotocin (single iv injection of 55 mg/kg) and given sodium orthovanadate in the drinking-water at a concentration of 0.6 - 0.8 mg/ml (corresponding to calculated daily intakes of between 75 ± 3 and 100 ± 3 mg/kg body weight per day, respectively) for 4 weeks, the serum-insulin level was low, but there was no increase in blood-glucose levels compared with controls. In diabetic rats not treated with vanadate, serum-insulin levels were also low, but blood-glucose levels were increased 3-fold. The cardiac performance of vanadate-treated animals did not differ significantly from that of non-diabetic controls. It was concluded that vanadate controlled blood-glucose levels and prevented the decline in cardiac performance due to diabetes.

The results of in vitro studies suggest that vanadium may play a specific physiological role as a regulator of the sodium pump (Macara, 1980). Vanadate has been shown to inhibit Na^+K^+-ATPase (EC 3.6.1.3) in intact human red blood cells (Rifkin, 1965; Cantley et al., 1977, 1978a,b). It also has potent diuretic and natriuretic effects in rats (Balfour et al., 1978; Westenfelder et al. 1981). It was a powerful inhibitor of Na^+K^+-ATPase in microsomal fractions of the kidney, brain, and heart in several species, including human beings (kidney). Mg^{2+}-ATPase was up to 10 000 times more resistant to vanadium inhibition than Na^+K^+-ATPase (Nechay & Saunders, 1978).

Similarly, *in vivo* studies on laying chickens fed calcium orthovanadate for 15 months, at levels of 0.25, 50, or 100 mg/kg diet, showed clear inhibition of Na^+K^+-ATPase activity in the kidney (Phillips et al., 1982). The inhibition of Na^+K^+-ATPase by vanadate can be reversed by catecholamines, though these do not have any effects on the Na^+K^+-ATPase activity in the absence of vanadate (Hudgins & Bond, 1979). The inhibition is also partially prevented by the reducing agents ascorbic acid and glutathione (Grantham & Glynn, 1979).

The mechanism by which cells reduce cytoplasmic $vanadium^{5+}$ to $vanadium^{4+}$ was investigated using human red cells (Macara et

al., 1980). The authors concluded that vanadate is reduced by cytoplasmic glutathione and that this explains the resistance of the Na^++K^+-ATPase to vanadium in intact cells.

Since vanadate (V^{5+}) is a potent inhibitor of Na^+K^+-ATPase, many physiological and biochemical processes are vanadium sensitive (Grantham, 1980; Nechay, 1984). For example, vanadium compounds inhibit ATP phosphohydrolases, ribonuclease, adenylate kinase, phosphofructokinase, squalene synthetase, glyceraldehyde-3-phosphate dehydrogenase (Macara, 1980), glucose-6-phosphatase (Singh et al., 1981), and phosphotyrosyl-protein-phosphatase (Swarup et al., 1982). The membrane neutral (K^+)-p-nitrophenylphosphatase in the membrane fraction of skeletal muscle was inhibited equally by vanadium^{4+} and vanadium^{5+} at 4 x 10^{-8} mol/litre (Vyskocil et al., 1981). Extracellular application of both forms of vanadium failed to inhibit the electrogenic (Na^+ - K^+) pump in intact mouse diaphragm fibres (Vyskocil et al., 1981). In the concentration range from 10^{-5} to 10^{-3} mol/litre, vanadium^{4+} even potentiated the hyperpolarization of the muscle fibres from -74 to -82 mV (Zemkova et al., 1982), probably by increasing the intracellular potassium level. These findings have led to the hypothesis that vanadate could control sodium pump activity *in vivo*, perhaps via a vanadium^{5+} : vanadium^{4+}, equilibrium connecting pump activity to the cellular redox state. However, vanadate in the red cell is reduced to vanadium^{4+}, which then binds to haemoglobin (Cantley & Aisen, 1979), a reaction that seems to be essentially quantitatively driven by glutathione (Macara et al., 1980), NADH (Vyskocil et al., 1980), or by other mild reducing agents, such as ascorbate or norepinephrine (Svoboda et al., 1984). The role of the vanadium^{5+} : vanadium^{4+} redox equilibrium in the regulation of cation flow across cell membranes has yet to be unequivocally demonstrated.

Vanadium appears to be essential for chicks and rats, but it does not appear to be essential in other species, as defined by Mertz (1970), i.e., an element is essential if its deficiency reproducibly results in an impairment of a function from optimal to suboptimal. However, more research is needed before definite conclusions can be drawn regarding the role of vanadium as a nutritionally essential trace element for animals.

5.2 Absorption

The absorption and distribution of vanadium compounds depend on the route of entry and the solubility of the compounds in body fluids. The solubility of vanadium compounds in biological media varies (Reznik, 1954). The following compounds are listed in decreasing order of solubility: (a) in gastric juices, vanadyl sulfate, sodium vanadate, ammonium vanadate, vanadium pentoxide; (b) in blood-serum and in 0.22% sodium carbonate solution, sodium vanadate, ammonium vanadate, vanadium pentoxide, and vanadyl sulfate. The higher the solubility in water and biological media, the more toxic the compound, presumably because of better absorption (Roshchin, 1968).

5.2.1 Absorption by inhalation

5.2.1.1 Human studies

There is little information on the deposition of vanadium compounds in the respiratory tract following inhalation. However, the greatest deposition would be expected in the submicrometre particle size fraction and particle size distribution studies (Lee et al., 1972) have shown that most vanadium-bearing particulate matter is very small and well within the respirable range for human beings.

Soluble vanadium compounds inhaled and deposited in the lung, are readily absorbed but the rates of absorption have not been quantified and estimates have not been made of the amounts of inhaled vanadium that are transported back to the pharynx by mucociliary clearance, swallowed, and are then available for absorption via the gastrointestinal tract. It has been estimated that about 25% of soluble vanadium compounds may be absorbed via the respiratory tract (ICRP, 1960). Absorption from the respiratory tract was demonstrated in workers exposed to vanadium dust, who showed increased concentrations of vanadium in the urine (Lewis, 1959b; Gylseth et al., 1979; Maroni et al., 1983).

5.2.1.2 Animal studies

Following acute exposure, there is complete clearance of the relatively soluble vanadium pentoxide from the lung within 1 - 3 days (Sjöberg, 1950; Levina, 1972). Stokinger et al (1953) demonstrated that vanadium is present for more than 40 days following cessation of long-term exposure.

Intratracheal administration of ^{48}V-vanadium nitrate (0.4 and 20 mg/kg body weight) to albino rats showed that the ^{48}V absorption rate was maximum after 5 min and could be detected in internal organs after 30 min. Blood levels were initially high, but fell to trace levels after 2 days. ^{48}V was not detectable after 4 days, but reappeared at 8 days and accumulated in all internal organs, the greatest quantity accumulating in the bone (Ordzhonikidze, 1977). In female Fischer rats exposed by intratracheal instillation to 40 µg vanadium pentoxide in 0.9% saline solution, the time for removal of 50% of the initial burden was 18 min, but traces remained for a considerable time. At 14 days, the vanadium was distributed principally in the carcass (40%) and skeleton (12%) (Rhoads & Sanders, 1985). In a study of the kinetics of vanadium following single or multiple intratracheal administration, the blood concentration was high initially and vanadium accumulated in the liver and kidney reaching the highest level after 24 h (Roshchin & Ordzhonikidze, 1986).

Vanadium trioxide was cleared from the lung more rapidly than pentoxide or ammonium vanadate following intratracheal instillation in rats (Levina, 1972).

5.2.2 Absorption from the gastrointestinal tract

5.2.2.1 Human studies

In general, vanadium salts are poorly absorbed from the human gastrointestinal tract. In a study by Curran et al. (1959), from 0.1 to 1% of 100 mg vanadium (as highly soluble

diammonium oxytartratovanadate) was absorbed from the gastrointestinal tract and 60% of this was excreted via the kidneys within 24 h. The remainder was retained in the liver and bone, until the oral administration ceased, when it was mobilized rapidly from the liver and slowly from the bone. Sodium metavanadate (12.5 mg/day for 12 days) was recovered largely unabsorbed in the faeces (87.6%) and the remainder in urine (12.4%) (Proescher et al., 1917). The International Commission on Radiological Protection (ICRP, 1960) estimate for the gastrointestinal absorption of soluble vanadium compounds was 2%. A low degree of absorption was also found by Roshchin et al. (1980).

5.2.2.2 Animal studies

Mountain (1959)[a] reported an unpublished study in which vanadyl sulfate was fed to adult male rats in daily doses ranging from 650 to 1250 µg (160 - 310 µg of vanadium). The mean absorption was about 0.5%, but urinary values varied considerably. The duration of the study was not given.

5.2.3 Absorption through the skin

Dermal absorption and skin irritation were reported in a study in which a nearly saturated solution (20%) of sodium metavanadate was applied to the skin of the rabbit (Stokinger, 1967).

However, according to US EPA (1977), the skin appears to be a minor route of vanadium uptake for human beings. In an in vitro study using ^{48}V radiotracer, there was no penetration of human skin samples (Roshchin, 1980).

5.3 Distribution and Transformation

5.3.1 Human studies

Vanadium levels in man, reported in earlier studies, were considerably higher than those reported more recently. The difference is illustrated by the whole-body content of 17 - 43 mg vanadium for a 70-kg man calculated by Schroeder (1963) compared with estimates of 100 µg derived by Byrne & Kosta (1978). The influence of different sampling procedures and analysis (colorimetric determination, neutron activation) should be clarified before concluding that such effects are real (Lagerkvist et al., 1986) or that they reflect decreasing environmental exposure.

[a] Mountain, J.T. (1959) Unpublished results, Toxicologic Services, Occupational Health Field Headquarters, Cincinnati, Ohio.

Absorbed vanadium is transported mainly in the plasma (Schroeder et al. 1963; Ordhzonikidze et al., 1977; Roshchin et al., 1980). Some mean values obtained using different methods of analysis are given in Table 17. There is a wide divergence in the results, the ratio between the highest and the lowest mean values being about 10^4. In general, levels tend to decline

chronologically as analytical techniques become more sensitive. There is also a difference in results obtained by neutron activation analysis according to whether separation was carried out before, or after, irradiation.

In an extensive investigation on human tissues, the inadequate sensitivity of the analytical method meant that quantitative information could only be obtained for the lung and intestine (Tipton & Cook, 1963). Using neutron activation analysis, Byrne & Kosta (1978) obtained information on other organs. Table 18 includes autopsy tissue values and some results from two other investigations using neutron activation analysis. It is apparent that vanadium concentrations are low in all tissues, though the liver, kidney, and lung often show higher levels than other tissues. In another investigation on a selection of organs, using spark-source mass spectrometry, the vanadium levels detected were: brain, 30 μg vanadium/kg wet weight (average from 10 specimens); liver, 40 μg/kg (average from 11 specimens); lung, 100 μg/kg (average from 11 specimens); lymph node, 400 μg/kg (average from 6 specimens); and testis, 20 μg/kg (average from 5 specimens) (Hamilton et al., 1972/73). The values reported are in reasonable agreement with those found in other animals. However, there is considerable disagreement between investigators and between analytical methods, which has not been resolved, since interlaboratory and intermethod investigations have not been carried out.

In the general population, which is mainly exposed to low levels of vanadium in food with poor absorption from the intestine, vanadium is usually undetectable in the urine, even using very sensitive methods (Byrne & Kosta, 1978). Examination of urine samples from 50 normal individuals using atomic absorption spectrometry showed that vanadium was present in only 13; 11 samples showed a level of 0.1 μg/litre and two, 0.2 μg/litre (Ueno & Ishizaki, 1980). In industry, where exposure is mainly through air and absorption from the lung is high, vanadium concentrations in the urine cover a considerable range (section 5.4.1).

Table 17. Vanadium levels in human blood[a,b]

Analytical method	Whole blood (mg/litre)	Serum/plasma (mg/litre)	Ref
X-ray emission		0.01 (43)	Gof
Spectrography	0.0078 (24)		Lif
Colorimetry	0.23 (calculated)	0.42 (13)	Sch
Neutron activation analysis (preseparated)	0.016		Bow
Neutron activation analysis		0.67 ± 0.32 ng/ml	Sim
Spectrography	0.126 (47)		But
Neutron activation analy-		0.0046 (36)	Hey

sis (preseparated)			
Catalytic	0.01 (82) 0.02 - 0.01 (7)		All
Spectrophotometric		0.057 (10)	Chr
Neutron activation analysis (preseparated)	0.0046		Kir
Neutron activation analysis (preseparated)	0.022 (5)		Buo
Neutron activation analysis (preseparated)	0.0005 (5)		Byr
Neutron activation analysis (preseparated)		0.0066[c] (5)	Sabi
Neutron activation analysis		0.000047 (9 males) 0.000024 (8 females)	Cor Cor
Neutron activation analysis		0.000033 (17 females)	Cor

[a] Adapted from: Byrne & Kosta (1978) and Versieck & Cornelis (1980).
[b] Number of subjects in parentheses.
[c] Recalculated values assuming an haematocrit of 0.45.

Table 18. Vanadium levels in human organs (μg/kg wet weight)[a]

Tissue	Study					
	Byrne & Kosta (1978)[b,c]			Damsgaard (1972)[c,d]		Lievens (1977)[b]
Kidney	3.3	3.2	2.6	nd	7	
Liver	7.5	4.5		5	19	7 - 19 (5)
Brain	0.7	0.75				
Thyroid	3.2	3.0				
Heart	1.1					
Cardiac fat	0.45	0.3				
Subcutaneous fat	0.63	0.80				
Muscle	0.45	0.62	0-59	7	nd	
Spleen				3	4	
Pancreas				nd	14	
Lung	19 - 40 (7)			nd	13	

median 30

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[a] From: Byrne & Kosta (1978).
[b] Parentheses enclose number of subjects.
[c] Brackets embrace specimens from one autopsy.
[d] nd = not detected.

Studies on vanadium levels in human bone have produced widely varying results. Byrne & Kosta (1978) reported the following data from human bones (lg/kg wet weight): skull, 2.5, 3, 4.5, 8.3; sternum, 3.1; rib, 0.8, 2.1; tooth enamel (fragmented), 2, 3.4, 4, 5.1; and tooth enamel (drill powdered), 18. The high concentration in tooth enamel may be due to diet; concentrations of vanadium tend to be higher in processed than in unprocessed foods (Myron et al., 1977), but vanadium is commonly present in steel alloys, especially tool steels, and vanadium contamination may have occurred from the drill. Using atomic absorption spectroscopy, Sumino et al. (1975) found a range of 100 - 200 μg/kg (wet weight) in 6 specimens of rib.

Using emission spectral analysis, Shevchenko (1965) detected a mean vanadium level of 150 ± 2 μg/kg (0.015 mg%) (dry weight) in 14 samples of healthy bone tissue; bone tumours contained higher levels.

Metal levels have been extensively studied in hair, because of its potential value for exposure and body burden studies. Gordus et al. (1974) and Gibson & DeWolfe (1979), using the same method as Byrne & Kosta (1978), found levels of 20 - 40 μg/kg in 42 subjects and 20 - 41 μg/kg in 370 subjects, respectively. These results compare favourably with those of Byrne & Kosta, i.e., 12 - 87 μg/kg in 12 subjects. Ueno & Ishizaki (1980) used atomic absorption spectrometry to determine vanadium in hair specimens from 130 men and 132 women. They found mean concentrations of 53.6 μg/kg (range, 5 - 155 μg/kg) and 44.2 μg/kg (range, 1.8 - 118.8 μg/kg), respectively. However, Creason et al. (1975), using emission spectroscopy in extensive surveys in the USA, found levels that were about 10 times higher.

There is considerable information on vanadium levels in lung tissue. In studies by Schroeder et al. (1963), vanadium was found in 97 out of 173 lungs examined in groups from 7 USA cities, group mean concentrations ranging from 10 to 130 μg/kg wet weight. Byrne & Kosta (1978) found levels of from 19 to 140 μg/kg (median, 30 μg/kg) in 7 cases; Hamilton et al. (1972/73) detected a mean level of 100 μg/kg in 11 cases; and Sumino et al. (1975) determined a range of 100 - 300 μg/kg for 13 observations. Statistical analyses of lung tissue trace metal data were performed by Tipton & Shafer (1964) using data taken from Tipton & Cook (1963). One approach was examination of the relationship between lung metal concentrations and age. The levels of a number of metals, including vanadium, increased in the lung with age, indicating accumulation of insoluble compounds, and Schroeder (1970b) calculated an annual increment rate of 1.3 μg for lung-vanadium. However, earlier analysis of the same data (Schroeder et al., 1963) did not show an age-related increase in lung-vanadium. The later analysis by Tipton & Shafer (1964) was performed on a subset of the original data

from Tipton & Cook (1963), which may account for some of the discrepancy. The Tipton & Shafer (1964) data did not show a graded increase in lung-vanadium with age, and there was a high mean level only in the oldest age group. This could have been produced by a single very high value in this age group. The concept of vanadium accumulation in the human lung with age remains doubtful, and the results of animal studies do not indicate significant accumulation in the lung (sections 5.1.1.2 and 5.3.2).

5.3.2 Animal studies

Observations on pregnant rats, that received vanadium on the 21st - 22nd day of pregnancy, revealed accumulation in the placenta but not "in perceivable quantities" in the organs of the fetus. Vanadium was reported to be secreted in the milk (Roshchin et al., 1980).

The identification of cellular components that react with vanadium has been investigated in vivo and in vitro using 48V radiotracer (Marafante & Sabbioni, 1983). Vanadium has a high affinity for nuclear and mitochondrial components. When rats were treated every day with 10 μg vanadium/rat for up to 8 days, a dose-related increase in vanadium incorporation in the subcellular fractions was observed. There is evidence that non-haem Fe-containing proteins, such as transferrin and ferritin, have a high affinity for vanadium, while Fe haemoproteins are not able to incorporate the metal.

In rat serum, both $Vanadium^{4+}$ and $Vanadium^{5+}$ form metal-protein complexes with transferrins. Specific intracellular vanadyl-ferritin complexes are formed in rat liver, spleen, and kidney (Chasteen et al., 1986).

Ermolaev (1969) studied the distribution of vanadium in the organs and tissues of 3 groups of rabbits, i.e., animals fed under ordinary conditions, animals fed a diet supplemented with vanadium (0.5% solution of vanadyl sulfate) at a dose of 0.05 mg/kg body weight, and animals fed the vanadium-supplemented diet and subcutaneously injected with vanadium also at 0.05 mg/kg body weight. The results of this investigation are given in Table 19. The method of administration had little effect on the resultant blood, brain, and stomach levels, but there were distinct differences in the case of the other organs and tissues.

The distribution and kinetics of vanadium, administered ip as 80 mg vanadocene dichloride/kg to strain A mice, were determined in blood, kidney, liver, small intestine, and brain. The vanadium concentration decreased rapidly and exponentially in the blood (half-time = 118 ± 43 min) and small intestine (half-time a = 18 ± 0.14 min; half-time b = 341 ± 45 min). Vanadium accumulated in kidney (maximum concentration, 1.12 ± 0.06 mmol at 12 h) and liver (maximum concentration, 0.56 ± 0.06 mmol at 8 h) and was then excreted (estimated half-time, 7.9 ± 0.7 h for kidney; 12.1 ± 0.1 h for liver). Vanadium was not detected in the brain (Toney et al., 1985).

Table 19. Vanadium levels in rabbit organs and tissues following oral and subcutaneous administration (mg %)[a]

Organ/ tissue	Control group	First group (0.05 mg/kg with food)	Second group (0.05 mg/kg with food and injected subcutaneously)
liver	66	88	632
muscle tissue	27	41	30
blood	29	82	90
spleen	68	116	180
kidneys	71	90	464
lungs	62	82	168
brain	20	26	24
heart muscle	52	68	71
intestine	20	22	32
stomach	30	70	74

[a] From: Ermolaev (1969).

The influence of the oxidation state of intravenously injected compounds of ^{48}V on uptake and distribution to selected organs and subcellular elements of the rat liver was studied by Hopkins & Tilton (1966). They did not observe any significant differences in the rate or amount of uptake of nanogram quantities of vanadium in three different oxidation states ($VOCl_3$, $VOCl_2$, and VCl_3) and concluded that either the oxidation state was not critical to transport or that the vanadium was converted to a common oxidation state in vivo. Similar results with respect to oxidation state and uptake and also the distribution of vanadium in the rat were reported by Sabbioni et al. (1978) and Conklin et al. (1982). In contrast, Parker & Sharma (1978) found that levels of vanadium in the tissues of male Wistar rats given sodium orthovanadate in the drinking-water at 50 mg/litre for 3 months were higher than those in the tissues of animals given vanadyl sulfate at the same concentration. Roshchin et al. (1964) found evidence of the partial conversion of vanadium trioxide to the pentavalent form in blood-serum and in weakly acidic and basic solutions in vitro. In a later study, Johnson et al. (1974) reported the in vivo conversion of vanadium pentoxide to the tetravalent state.

Information on vanadium distribution in rats after intraperitoneal, intratracheal, oral, and subcutaneous administration of radioactive (^{48}V) vanadium nitrate in single doses of 20 mg/kg body weight (LD_{50}) and 0.4 mg/kg body weight (non-toxic

dose) is given in Table 20 (Roshchin et al., 1980). The study, which involved 1060 albino rats, showed that whatever the method of administration, vanadium was present in blood in significant quantities only during the first 24 h, and that, after 2 days, only traces of vanadium were detectable. No vanadium was found in the blood after 4 - 8 days. However, in the groups administered the radioactive compound intratracheally or subcutaneously, low amounts of vanadium were detected between 8 and 16 days after administration as a result of reabsorption from the organs. The highest level occurred 5 min after intratracheal administration, 30 min after intraperitoneal administration, and 15 min - 1 h after subcutaneous or intragastric administration. Vanadium was detected in all tissues and organs. In 2 days, vanadium had accumulated in the bone, kidney, liver, and lung, which were also the primary targets in rats after intratracheal administration of vanadium pentoxide ($^{48}V_2O_5$) or chloride ($^{48}VO_2Cl$) (Conklin et al., 1982) and after oral administration of vanadyl sulfate or sodium orthovanadate in the drinking-water (50 mg/litre) for three months (Parker & Sharma, 1978).

In another study, $^{48}VOCl_3$, which is fairly soluble, was administered intratracheally to juvenile male Wistar rats at a dose of 12.6 μCi in 1 ml buffered solution. Within 15 min, the vanadium isotope was found in all major organs, except the brain. The largest fractions were found in the blood, heart, spleen, liver, and kidneys. Peak uptake occurred between 4 and 24 h after administration and activity was maintained throughout a 9-week period (Oberg et al., 1978).

5.4 Retention

5.4.1 Human studies

Vanadium levels in human tissues (Table 18, section 5.3.1) are low, the highest concentrations tending to occur in the liver, kidney, and lung.

Storage of available vanadium in man occurs mainly in fat and serum lipids (Schroeder et al., 1963).

Shevchenko (1965) used emission spectral analysis to determine the vanadium contents of bone tumours and of the cortical layer of bone adjacent to the tumours. He found that vanadium accumulated in tumours. Healthy bone tissue contained a mean vanadium concentration of 0.15 ± 0.002 mg/kg dry weight, osteoblastomas contained 6.38 ± 1.17 mg/kg, and osteosarcomas, 4.16 ± 0.77 mg/kg. The cortical layer adjacent to osteoblastomas contained 2.01 ± 0.42 mg/kg, and that adjacent to osteosarcomas contained 1.77 ± 0.48 mg/kg. In comparison to normal bone, bone cysts, osteochondromas, and exostoses also showed higher vanadium levels, but to a lesser extent than bone tumours.

The significant accumulation of vanadium in the tissue of benign and malignant tumours and, to a lesser extent, in the neighbouring tissue suggests that quantitative changes in the amounts observed may indicate disturbances in its metabolism. This may be in connection with the role of vanadium in the

phospholipid and cholesterol metabolism, which may become indirect indicators of the intensity of the phospholipid turnover in tumour tissue.

5.4.2 Animal studies

Large amounts of vanadium were reported in the crude fat from beef, pork, and lamb (Schroeder et al., 1963), but the results of subsequent studies do not support this finding, which is probably erroneous because of the analytical methods used (NRC, 1980).

In rats, after oral administration of 20 mg vanadium nitrate/kg body weight, levels of vanadium in the blood were detectable only during the first 24 h, and only traces remained after 48 h; after 4 days, no vanadium was found in blood. For 48 h after the administration of vanadium, concentrations in the organs increased by 0.4% of the administered dose in the liver, by 0.69% in the kidneys, and by 0.16% in the spleen. The most significant increase in vanadium (1.01% of the dose administered) was found in the bones. After 16 days, the level in the bone tissue had increased by 1.72% of the dose administered, while in other organs it had significantly decreased (Roshchin et al., 1980).

Studies on rats showed that liver, kidney, spleen, and testes continued to accumulate intravenously injected vanadium-48 for up to 4 h and that most of the radioactivity was retained for up to 96 h (Hopkins & Tilton, 1966). After 96 h, 14 - 84% of the 10-min uptake was retained in other organs, and 46% and 9% of the vanadium-48 had been eliminated in the urine and faeces, respectively. Levels of vanadium-48 in the mitochondrial and nuclear fractions of homogenized liver increased from 14 to 40% of the total during the first 96 h, while the level of radioactivity in the microsomal fraction remained relatively constant.

When strain A mice were given 80 mg vanadocene dichloride/kg ip, vanadium accumulated in the liver and kidney. Maximum concentrations of 1.12 ± 0.06 mmol in the kidney and 0.56 ± 0.06 mmol in the liver were reached after 12 h and 8 h, respectively (Toney et al., 1985).

Table 20. Concentrations of ^{48}vanadium in the organs and tissues of rats after intra subcutaneous, intratracheal, and intragastric administration of a radioactive vanadi (expressed as % radioactivity equivalent to 10 uCi per animal)[a]

Organ/tissue	Intraperitoneal administration			Intratracheal administr	
	Time after administration				
	30 min	2 days	16 days	30 min	2 days
Liver	2.20 ± 0.55	0.43 ± 0.02	0.22 ± 0	0.43 ± 0.19	0.36 ± 0.19
Kidney	7.20 ± 0.85	1.60 ± 0.02	0.66 ± 0	1.55 ± 0.67	1.56 ± 0.19
Spleen	2.16 ± 0.23	0.17 ± 0.01	0.09 ± 0	0.15 ± 0.06	0.18 ± 0.02
Lung	2.53 ± 0.73	0.11 ± 0	0	9.09 ± 5.91	0.20 ± 0.39
Stomach	2.93 ± 0.73	0.08 ± 0	0	2.56 ± 0.94	0.13 ± 0.05
Small intestine	2.53 ± 0.31	0.08 ± 0	0	0.71 ± 0.22	0.21 ± 0.15
Large intestine	3.33 ± 0.88	0.13 ± 0.03	0	0.19 ± 0.08	0.17 ± 0.05
Muscle	0.40 ± 0.05	0.03 ± 0	0	0.28 ± 0.20	0.03 ± 0

Bone	2.13 ± 0.12	3.45 ± 0.48	1.72 ± 0.31	0.79 ± 0.31	2.19 ± 0.31
Testicle	1.30 ± 0.15	0.09 ± 0	0.06 ± 0	0.09 ± 0	0.08 ± 0
Thyroid gland	0.60 ± 0	0.23 ± 0.05	0	1.21 ± 0.69	0.54 ± 0.40
Adrenals	2.53 ± 1.01	0.11 ± 0.02	0	0.67 ± 0	0.06 ± 0.02
Pancreas	7.88 ± 0.26	0.31 ± 0.06	0	0.14 ± 0.04	0.08 ± 0.02
Brain	0.16 ± 0.04	0.01 ± 0	0	0.02 ± 0	0
Heart	1.50 ± 0.34	0.07 ± 0	0	0.04 ± 0	0.08 ± 0

Table 20 (contd.)

Organ/tissue	Intragastric administration			Subcutaneous adminis	
	Time after administration				
	30 min	2 days	16 days	30 min	2 days
Liver	0.08 ± 0.03	0.33 ± 0.11	0.27 ± 0	0.05 ± 0.01	1.00 ± 0.15
Kidney	0.17 ± 0.13	0.69 ± 0.20	0.67 ± 0	0.13 ± 0.03	2.30 ± 0
Spleen	0.04 ± 0	0.16 ± 0.05	0.08 ± 0	0.03 ± 0	0.31 ± 0.03
Lung	0.06 ± 0.02	0.09 ± 0.01	0.06 ± 0	0.10 ± 0.01	0.19 ± 0.01
Stomach	8.08 ± 1.49	1.55 ± 0.05	0.05 ± 0	0.29 ± 0.01	0.12 ± 0
Small intestine	4.65 ± 9.95	0.22 ± 0.09	0.06 ± 0	0.77 ± 0.66	0.11 ± 0.01
Large intestine	0.12 ± 0	0.14 ± 0	0.01 ± 0	0.46 ± 0.21	0.14 ± 0
Muscle	0.01 ± 0	0.02 ± 0	0.04 ± 0	0.40 ± 0.30	0.03 ± 0
Bone	0.05 ± 0.02	1.01 ± 0.31	1.72 ± 0	0.43 ± 0.30	3.23 ± 0.41
Testicle	0.26 ± 0.20	0.04 ± 0	0.06 ± 0	0.01 ± 0	0.12 ± 0.01
Thyroid gland	0.08 ± 0	0.32 ± 0.24	0	0.15 ± 0.05	0
Adrenals	-	0.09 ± 0.03	0	0.10 ± 0	0.16 ± 0.04
Pancreas	0.32 ± 0.29	0.04 ± 0.04	0.08 ± 0	0.03 ± 0	0.09 ± 0.01
Brain	0.02 ± 0	0.01 ± 0	0.02 ± 0	0.03 ± 0	0.02 ± 0
Heart	0.06 ± 0	0.05 ± 0	0	0.06 ± 0	0.12 ± 0

[a] From: Roshchin et al. (1980).

In a study on 2 young rats (strain unspecified), the highest uptake of vanadium-48 from V_2O_5 occurred in rapidly mineralizing areas of dentine and bone (Söremark et al., 1962). In mice, high uptake occurred in the mammary glands, liver, renal cortex, and lung (Söremark & Ullberg, 1962).

In studies by Belehova (1966, 1969), vanadium levels were lower in carious than in normal canine teeth. In other studies, intramuscular injection of vanadium in dogs at a dose of 2 mg/kg body weight resulted in vanadium levels in the hard tissues of the teeth that were 1.3 times higher than those in the controls. On the 7th day, the concentration in the enamel had almost returned to its initial level of 8.8 mg/kg; the level in the dentine was still 32% higher.

Vanadium was reported to decrease the incidence of dental caries, when added to the diet of hamsters (Geyer, 1953). However, Hein & Wisotzky (1955) reported significant increases in dental caries in hamsters given drinking-water containing vanadium pentoxide equivalent to 10 mg vanadium/litre over an 80-day period. Muhler (1957) studied the effect of vanadium pentoxide on caries in Sprague-Dawley rats. Groups of 50 rats received vanadium (as vanadium pentoxide) at 10 mg/litre, 20 mg/litre, or 40 mg/litre in their drinking-water. One control group received drinking-water containing ammonium fluorosilicate (20 mg/litre), the other received untreated water. Vanadium did not produce any reduction in the incidence

of dental caries, in fact there was a slight, but not significant increase in dental caries in the groups receiving 10 mg/litre and 20 mg/litre for 140 days. All the rats showed signs of vanadium toxicity and all animals in the highest dose group (40 mg/litre) died within 65 days.

In an in vitro study on the effects of vanadate on bone formation in 21-day-old fetal rat calvariae, sodium vanadate at concentrations of 0.1 - 10 mmol stimulated the incorporation of ^{3}H-thymidine into DNA and increased the bone DNA content and the mitotic index. Sodium vanadate at a concentration of 100 mmol produced a marked and irreversible inhibition of DNA labelling and protein synthesis. Concentrations of 1 mmol (24 h) and 10 mmol (96 h) inhibited alkaline phosphatase activity. Sodium vanadate also stimulated collagen and non-collagen protein at low concentrations, but again had an irreversible inhibitory effect at a high concentration of 100 mmol (Canalis, 1985).

5.5 Elimination

5.5.1 Human studies

Owing to low gastrointestinal absorption, ingested vanadium is predominantly eliminated unabsorbed in the faeces. The principle route of excretion of absorbed vanadium is through the kidneys.

The relationship between urinary excretion and the extent of exposure has been studied. As part of a clinical study on the effects on cholesterol level, Dimond et al. (1963) gave ammonium vanadyl tartrate to patients (5 female, 1 male) and did not find any correlation between urinary excretion and oral dose. Variable absorption was suggested as the reason for wide variation in urinary excretion. In a 50-week study on 2 volunteers, Tipton et al. (1969) reported a urine/diet ratio of 0.13. This is in agreement with the figure of 12.4% excretion in urine in a man given sodium metavanadate orally (12.5 mg daily for 12 days) (Proescher et al., 1917).

Studies on occupationally exposed populations have shown a poor correlation between vanadium concentrations in air and amounts excreted in urine (Williams, 1952; Lewis, 1959b; Jaraczewska & Jakubowski, 1964; Watanabe et al., 1966; Troppens, 1969; Köhler, 1972). Differences in laboratories and methods may contribute to the wide range of urinary concentrations reported.

In a study on power-station workers exposed to vanadium during maintenance work on an oil-fired boiler, it was shown that urinary excretion increased in those most heavily exposed, in spite of the use of protective masks. For instance, urinary levels of vanadium in 6 welders and 4 cleaners increased over a work shift from 2.7 to 43.8 mg vanadium/kg creatinine and from 1.65 to 52.8 mg/kg, respectively. The vanadium concentration in air during boiler cleaning was estimated to vary between 0.1 and 5 mg/m^{3} (Maroni et al., 1983). These results resemble those reported by Thürauf et al. (1979) on 54 workers exposed to vanadium in a metallurgical plant. Exposed workers had a urinary vanadium concentration of 33.9 mg/kg creatinine, whereas the level in unexposed workers was 0.6 mg/kg creatinine.

Roshchin et al. (1980) used polarography in a study of the urine samples of 100 workers who were exposed daily to vanadium pentoxide, and found vanadium in 50% of subjects. The mean concentration of vanadium in the urine was 0.18 ± 0.03 mg/litre. In workers with a duration of exposure in the range of 1 - 2 years, the mean concentration was 0.14 ± 0.08 mg/litre; after 2 years, the mean concentration was 0.20 ± 0.009 mg/litre. In workers employed for 2 - 6 months, the mean concentration of vanadium in the urine was 0.16 ± 0.12 mg/litre. There appeared to be a correlation between the urinary levels and the concentration of vanadium in the air. For example, in workers exposed to mean vanadium pentoxide atmospheric concentrations of 0.28 ± 0.06 mg/m^3, the concentration in the urine was 0.20 ± 0.05 mg/litre; at an atmospheric concentration of 0.17 ± 0.01 mg/m^3, the urinary concentration was 0.19 ± 0.007 mg/litre.

The relationships between personal exposure and blood and urine levels of vanadium were examined in 16 workers in a ferrovanadium plant in Norway (Gylseth et al., 1979). Individual levels did not show any clear relationship between exposure and response, but, when the data were divided into high- and low-exposure groups, significant differences were found for both blood and urine levels in relation to exposure levels. There was also a reasonably good correlation between blood and urine levels. However, the authors concluded that "the differences are small and the method difficult and expensive, so for a routine control other criteria should be sought".

Kiviluoto et al. (1979a,c) studied serum- and urinary-vanadium levels in relation to exposure levels. Grouped and individual data were examined at intervals during vacation periods and compared with those for an unexposed group. The levels of exposure were low (0.01 - 0.05 mg/m^3), and no correlations between exposure levels and serum or urine concentrations were found. However, there was a conspicuous decline in the urine levels at the beginning of the vacation period, but they did not decline down to the level of the unexposed group. It was considered that this provided some measure of the extent of exposure.

5.5.2 Animal studies

Talvitie & Wagner (1954) administered sodium metavanadate monohydrate in saline to albino Webster rats and albino rabbits by intraperitoneal and intravenous injection, respectively. In one part of the study, rats were given a single ip dose equivalent to 0.5 mg vanadium/kg body weight and, in another, twice daily ip injections, each equivalent to 0.25 mg vanadium/kg body weight, for 5 days. Rabbits were injected intravenously twice daily for a total of 7 or 9 days, with doses equivalent to 0.25 mg vanadium/kg body weight, except for 1 rabbit that received doses of 0.4 mg/kg body weight for the second 5-day period. No histological changes were noted. The ratio of vanadium eliminated in the urine and faeces was 5:1.

Following oral administration of vanadium sulfate and

vanadium pentoxide to guinea-pigs (equivalent to 2 mg vanadium/kg body weight), Reznik (1954) found vanadium in the urine and faeces for 7 - 10 days, though elimination in the urine ceased before that in faeces. The author concluded that the presence of vanadium in the faeces, several days after administration, was due to its return to the intestine after internal resorption and excretion. Biliary excretion of less than 2% of the intravenously injected dose (between 0.9 and 30 μg pentavanadate/kg body weight) was demonstrated in rats during the first 6 h after administration. By comparison, 20% was excreted with the urine during the same period of time (Sabbioni et al., 1981).

Roshchin (1968) administered a dose of 3 mg vanadium trichloride to 180-g albino rats. Most of the vanadium was excreted via the kidneys. Of the dose administered, 18% was found in the urine after 24 h and 25%, after 48 h. The amount of vanadium excreted in the urine fell and, after 6 days, was low. Elimination of vanadium via the intestine occurred on a much smaller scale and remained relatively stable; 30.9% of the administered dose was excreted over a 6-day period. Thus, the largest quantity of vanadium was eliminated during the first 2 days, and the rest was eliminated gradually. The ratio of amounts eliminated in the urine and faeces was 5:1, corroborating the findings by Talvitie & Wagner (1954).

In a study on mice, rats, and dogs, Mitchell & Floyd (1954) showed that ascorbic acid increased vanadium elimination in the urine during the first few days and later in the faeces. $CaNa_3DTPA$ (salicylic salt of diethylenetriamine-pentaacetic acid) increased vanadium excretion in the urine and reduced elimination via faeces. Following the combined administration of both preparations, elimination in the faeces increased.

6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

6.1 Aquatic Organisms

6.1.1 Microorganisms and higher plants

Trace quantities (1 - 10 μg/litre) of vanadium stimulated the growth of some algae, including Scenedesmus or Chlorella (Arnon & Wessel, 1953; Hopkins et al., 1977; Patrick, 1978). Toxicity studies on phytoplankton, mainly using pentavalent vanadium, have revealed differences in susceptibility between various species. A concentration of 0.02 mg/litre, as ammonium vanadate, interfered with the cell division of the fresh-water algae Chlorella pyrenoidosa, whereas 0.25 mg/litre was lethal (Meish & Benzschawel, 1978). The 15-day LC_{50} for an estuarine and salt-water green alga (Dunaliella marina) was given as 0.5 mg/litre of sodium metavanadate and that of a salt-water pennote diatom (Asterionella japonica) as 2 mg/litre (Minamand & Unsal, 1978).

Vanadium does not appear to be essential for higher plants.

6.1.2 Invertebrates

In a study using sea-water with a background level of 0.0017 mg vanadium/litre, the 9-day LC_{50}s for vanadium (as sodium metavanadate) for the worm (Nereis diversicolor), mussel (Mytilus galloprovincialis), and crab (Carcinas maenas) were 10, 35, and 65 mg vanadium/litre, respectively (Miramand & Unsal, 1978). Some marine invertebrates, such as the tunicates, accumulate vanadium to levels that may be 10^{-5} to 10^{-6} times the sea-water concentrations (Table 3.). Vanadium levels in such species may exceed 3000 mg/kg dry weight (Biggs & Swinehart, 1976; Carlson, 1977). It was stated that the uptake of vanadium by the mussel (Mytilus edulis) from food (plankton) was of the same magnitude as that from water (Unsal, 1978). It appears that benthic aquatic organisms tolerate higher concentrations of vanadium than fish (section 6.1.3).

6.1.3 Fish

There are some data on the acute toxicity of vanadium for fish (Van Zinderen Bakker & Jaworski, 1980). The 4- to 6-day LC_{50}s for fresh-water species are in the range 0.5 -10 mg/litre. Factors influencing toxicity include water hardness, and the LC_{50} values are higher in hard water. Giles et al. (1979) studied the influence of pH on the toxicity of vanadium pentoxide for rainbow trout fingerlings. The 96-h LC_{50} ranged from 6.43 to 21.75 mg/litre. There was some indication of vanadium pentoxide being most toxic at a pH of 7. Also, Sprague et al. (1978) tested zebrafish *(Brachydanio rerio)* with vanadium pentoxide and found that a pH of 7.5 provided the most toxic conditions. At this pH, death occurred between 23.5 and 45 h at a concentration of 22 mg/litre, whereas at pH 8.2, the time decreased to 32 h and, at pH 8.8 - 9, to 37 - 39 h.

Studying the chronic effects of vanadium pentoxide on flagfish, Sprague et al. (1978) and Holdway & Sprague (1979) concluded that the sublethal threshold concentration would be about 0.08 mg vanadium/litre.

The rainbow trout *(Salmo gairdneri)* is the most commonly used fish for toxicity studies. Sprague et al. (1978) reported 7-day LC_{50} values in one series of studies ranging from 2.4 to 5.6 mg/litre. Increasing the exposure time resulted in progressively lower LC_{50} values, the lowest being 1.99 mg/litre for an 11-day exposure period. Similar results were reported by Giles et al. (1979) using experimental conditions of pH 8, 15 °C, and hardness 90 mg $CaCO_3$/litre. The LC_{50} values decreased from 4.34 mg $CaCO_3$/litre for 5 days exposure to 1.95 mg $CaCO_3$/litre for 14 days. Neither of these groups was able to define a minimum lethal level for rainbow trout. Studies by Stendahl & Sprague (1982) indicated that small rainbow trout were more resistant than larger fish to vanadium pentoxide. In general, rainbow trout eggs were 10 - 15 times more resistant to pentavalent vanadium than fingerlings, suggesting the possibility of a protective function by the chorion (Giles et al., 1979). It should be noted that the available studies on vanadium toxicity have been performed on fresh-water species only. The effects of salinity remain to be studied.

6.2 Terrestrial Organisms

6.2.1 Uptake of vanadium by plants

In general, the highest concentrations of vanadium in plants growing in natural soils occur in the roots and decrease towards the aerial portions of the plant. The concentration of vanadium in soil is, by and large, 10 times the concentration in the plant (Cannon, 1963). Absorption appears to be passive (Welch, 1973).

When grown in culture solution, several plant species absorb vanadium, which is also translocated to the aerial parts and seeds (Hopkins et al., 1977).

6.2.2 Effects on plants

Vanadium has not been demonstrated to be essential for higher land plants (Hopkins et al., 1977). However, traces of vanadate (0.02 mmol vanadium as VO^{2+} or VO_3^-) were shown to promote chloroplast development and oxygen production in higher plants. Vanadium also had a function as a redox catalyst in the electron flow from photosystem II to photosystem I (Meisch & Becker, 1981).

Small amounts of aqueous vanadium (10 - 20 mg/litre) have detrimental effects on most plants (Cannon, 1963). The growth of flax, peas, soybeans, and cabbage was reduced in nutrient solutions containing 0.5 mg vanadium/litre (given as $VOCl_2$ or VCl3) (Warington, 1955; Hara et al., 1976). Vanadium can induce iron deficiency chlorosis (Cannon, 1963) or affect the trace element nutrition by reducing the levels of, e.g., manganese, copper, calcium, and phosphorus (Warington, 1955; Wallace et al., 1977). Similarly, 5 mg vanadium/litre (as VO_3^-) in irrigation water reduced the growth of sugar beets by 30 - 50% and caused iron deficiency chlorosis (Hewitt, 1953).

In soils, the toxicity of vanadium may range between 10 and 1258 mg/kg, depending on plant species and type of soil (Hopkins et al., 1977). Ten mg/kg added to sandy soil as $Ca(VO_3)_2$ decreased the growth of sour orange, whereas 150 mg/kg was lethal (Vanselow, 1950).

Fertilizers may have a high vanadium content. For instance, rock phosphate, super phosphate, and basic slag may contain several thousand mg vanadium/kg. These may cause unacceptable levels of accumulation of vanadium in soil (Mitchell, 1964; Hopkins et al., 1977). Urban sewage sludges usually contain less than 35 mg/kg of vanadium (Bradford et al., 1975; Oliver & Cosgrove, 1975). On the other hand, vanadium in sewage sludge may be up to 6 times more easily available in sludge than in soil (Bernow & Webber, 1972).

7. EFFECTS ON EXPERIMENTAL ANIMALS AND *IN VITRO* TEST SYSTEMS

7.1 General Toxicity

The toxicity of vanadium for experimental animals varies with the species and route of administration. Smaller animals,

including the rat and mouse, tolerate the metal well; the rabbit and horse are more sensitive (Hudson, 1964). In general, toxicity is low when the metal is given by the oral route, moderate by the respiratory route, and high by injection. Lethal doses for various vanadium salts injected intravenously in rabbits and subcutaneously in guinea-pigs, rats, and mice are shown in Table 21.

Table 21. Lethal doses of vanadium (mg V_2O_5/kg body weight) in experimental animals[a]

Compound	Rabbit[b]	Guinea-pig	Rat	Mouse
colloidal vanadium pentoxide	1 - 2	20 - 28	-	87.5 - 117.5
ammonium metavanadate	1.5 - 2	1 - 2	20 - 30	25 - 30
sodium orthovanadate	2 - 3	1 - 2	50 - 60	50 - 100
sodium pyrovanadate	3 - 4	1 - 2	40 - 50	50 - 100
sodium tetravanadate	6 - 8	18 - 20	30 - 40	25 - 50
sodium hexavanadate	30 - 40	40 - 50	40 - 50	100 - 150
vanadyl sulfate	18 - 20	34 - 45	58 - 190	125 - 150
sodium vanadate	-	30 - 40	10 - 20	100 - 150

[a] From: Hudson (1964).
[b] Rabbits were injected intravenously; other animals subcutaneously.

The toxicity of vanadium also varies considerably with the nature of the compound, vanadium being toxic both as a cation and as an anion. As a general rule, toxicity increases as valency increases, vanadium^{5+} being the most toxic. Among the oxides of vanadium, vanadium pentoxide is more soluble and more toxic than the trioxide or dioxide.

Roshchin (1967b, 1968) described the results of acute inhalation studies on albino rats exposed to vanadium pentoxide in the form of a condensation aerosol (fume) at 10 - 70 mg/m^3 or in the form of a dispersion aerosol (dust) at 80 - 700 mg/m^3, ammonium vanadate (presumably as a dispersion aerosol) at 1000 mg/m^3, and ferrovanadium, as a dispersion aerosol at 1000 - 10 000 mg/m^3. The minimum concentration of vanadium pentoxide (condensation aerosol) that gave rise to mild signs of acute poisoning was 10 mg/m^3 air. The absolute lethal concentration for the condensation aerosol was 70 mg/m^3. Dispersion aerosols (containing large particles) were only one-fifth as toxic as condensation aerosols. Inhalation of dispersion aerosols of ferrovanadium did not produce any acute toxic effects, probably because the particles were too large. However, acute toxic effects were observed following intratracheal instillation of

ferrovanadium. These may have been related to the biological solubility and the extent of absorption.

The effects of vanadium on experimental animals have been investigated in a number of studies using various compounds, species, and test protocols. Some representative acute and long-term studies are summarized in Tables 22 and 23. Subsequent discussions on the effects of vanadium on specific biological systems are frequently based on the results of these studies.

7.2 Effects on Metabolic Processes

Rabbits exposed to a dispersion aerosol of vanadium trioxide (40 - 75 mg/m^3, 2 h/day for up to 12 months) exhibited a progressive weight loss amounting to an average of 4.6% at the termination of the study. Control animals gained weight by an average of 12.3%. The number of white blood cells declined by the end of the test from between 7000 and 8000 down to 5000/mm^3; no change was noted in controls. Haemoglobin levels in the test animals decreased from 75 to 68% of normal levelsa. Serum-ascorbate levels in the blood progressively decreased to about 20% of controls between 7 and 8 months. Protein sulfhydryl levels in the serum of exposed animals decreased by 30% compared with those of the controls. Respiration in the liver and brain tissues of test animals was reduced by one-half by the end of the study compared with controls, but the respiratory quotient was unchanged. Blood-cholinesterase levels in exposed rabbits increased by an average of 25% after the fifth month (Roshchin et al., 1964; Roshchin, 1968).

In these studies, the weight loss together with the depression in levels of white cells, haemoglobin, and protein sulfhydryl groups in the blood and the decreased liver tissue respiration were taken as indicators of the "general toxic effect" of vanadium. Increased cholinesterase activity was held to be indicative of sensitization.

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[a] Normal haemoglobin level in the rabbit is 80 - 150 g/litre and normal rabbit haematocrit, 30 - 50%.

Table 22. Acute studies on experimental animals

Compound	Species	Route of administration	Dose index	Concentration or dose
vanadium pentoxide	mouse	intragastric	LD_{50}	23.4 mg/kg body weight
	rat	inhalation	LC_{50}	70 mg/m^3
	rat	inhalation	minimum effective	10 mg/m^3
	rat	inhalation	LC_{50}	70 mg/m^3
	cat	inhalation	LC_{50}	500 mg/m^3
	rabbit	inhalation	LC_{100}	205 mg/m^3
	rat	intragastric	LD_{100}	10 mg/kg body weight
ammonium vanadate	mouse	intragastric	LD_{50}	10 mg/kg body weight

	rat	intragastric	effective	20 mg/kg body weight
	rat	subcutaneous	effective	5-30 mg/kg body weight
vanadium trichloride	mouse	intragastric	LD_{50}	24 mg/kg body weight
vanadium di-iodide	mouse	intragastric	LD_{50}	68 mg/kg body weight
vanadium dibromide	mouse	intragastric	LD_{50}	88 mg/kg body weight
vanadium trioxide	mouse	intragastric	LD_{50}	130 mg/kg body weight
ammonium metavanadate	rat	intragastric	LD_{50}	10 mg/kg body weight
vanadyl sulfate	rat	intragastric	LD_{100}	10 mg/kg body weight
	rabbit	subcutaneous	LC_{50}	59.1 mg/kg body weight
	rabbit	subcutaneous	maximum tolerated	25 mg/kg body weight
	guinea-pig	subcutaneous	LD100	800 mg/kg body weight
	guinea-pig	subcutaneous	LD_{50}	560 mg/kg body weight
	guinea-pig	subcutaneous	maximum tolerated	300 mg/kg body weight
water-soluble vanadium compounds	mouse	intragastric	LD_{50}	5 mg/kg body weight
	mouse	intragastric	no effect	0.005 mg/kg body weigh (or 0.1 mg/litre in water)

Table 23. Long-term studies on experimental animals

Compound	Species	Route of administration	Concentration	Duration of exposure	Ref
vanadium pentoxide	rabbit	inhalation	20 - 40 mg/m^3	several months	Sjö
	rabbit	inhalation	25 mg/m^3	10 months	Gul
	guinea-pig	inhalation	25 mg/m^3	10 months	Gul
	rabbit	inhalation	8 - 18 mg/m^3	9 - 12 months	Ros
	rat	oral	5 - 30 mg/kg	6 months	Ros
	rat	inhalation	10 - 30 mg/m^3	several months	Ros
	rat	inhalation	3 - 5 mg/m^3	several months	Ros
	rat	inhalation	0.027 mg/m^3	70 days	Paz
	rat	inhalation	0.002 mg/m^3	70 days	Paz
	rat	inhalation	0.006 mg/m^3	40 days	Paz
ammonium metavanadate	rat	subcutaneous	1 mg/kg	30 days	Kak
sodium metavanadate	guinea-pig	subcutaneous	3.2 - 128 ug/kg	days	Kul
	guinea-pig	subcutaneous	5.12 mg/kg	days	Kul
vanadium trioxide	rabbit	inhalation	40 - 75 mg/m^3	9 - 12 months	Ros

	rat	oral	5 - 30 mg/kg	6 months	Ros
vanadium trichloride	rabbit	oral	5 mg/kg	2 - 3 months	Ros
vanadium carbide	rabbit	inhalation	40 - 80 mg/m^3	9 - 12 months	Rosi
	rat	oral	5 - 30 mg/kg	6 months	Ros
	rat	intratracheal	25 mg per rat	9 - 12 months	Ros
ferrovanadium	rat	intratracheal	25 mg per rat	9 - 12 months	Ros
metallic vanadium	rat	intratracheal	25 mg per rat	9 - 12 months	Ros

Chronic poisoning, following the inhalation of trivalent vanadium (V_2O_3) or the oral administration of vanadium trichloride (VCl_3), resulted in blood changes by the end of the second and third months (Table 24). These changes were characterized by decreased albumin and increased globulins (mainly y-globulins) with a halving of the albumin-globulin ratio, and by an increase in serum concentrations of the amino acids cystine, arginine, and histidine. There was also a 10% increase in nucleic acid levels in the blood and a "considerable" increase in the blood-chloride concentration. The effects of vanadium on the metabolism of proteins and nucleic acids were considered to be responsible for the immunological and allergic reactions that may occur in vanadium poisoning (Roshchin, 1967a).

Metabolic changes were observed in a study by Pazhynich (1966) in which albino rats were exposed by inhalation for 70 days to condensation aerosols of vanadium pentoxide at levels of 0.027 ± 0.002 mg/m^3 and 0.002 ± 0.00013 mg/m^3. Statistically significant changes were observed at the higher level of exposure, but not at the lower level. The observations included decreases in: whole blood-cholinesterase levels, total serum-protein levels, serum-globulin levels, and the oxyhaemoglobin content of venous blood. Elevated serum-globulin levels, increased numbers of blood leukocytes showing yellow, orange, and red nuclear fluorescence with acridine orange, and increased oxygen consumption as indicated by isolated liver preparations were also observed in the high-level exposure group. The pattern of leukocyte nuclear fluorescence returned to normal 20 days after cessation of exposure. In a second study, albino rats were continuously exposed to vanadium pentoxide at 0.006 ± 0.00056 mg/m^3 for 40 days. No changes in blood-leukocyte nuclear fluorescence were observed. During the sixth week of exposure, animals received water but no food. After 3.5 days of this treatment, the number of leukocytes displaying altered nuclear fluorescence increased by a factor of 4.83.

In an *in vitro* study, ammonium metavanadate was found to inhibit microsomal ketamine *N*-demethylation, lipid peroxidation, and hydrogen peroxide formation in rat liver. The inhibiting doses of NH_4VO_3 ranged from 10^{-5} to 10^{-3} mol/litre. Cytochrome c reductase was also inhibited, whereas cytochrome oxidase activity was stimulated (Beyhl, 1983).

Parenteral injection of guinea-pigs with sodium metavanadate in daily doses of 3.2 µg/kg, 128 µg/kg, or 5.12 mg/kg body

weight resulted in dose-dependent increased succinate dehydrogenase activity in the liver and kidneys and cytochrome oxidase activity in the liver (Kulieva, 1974).

Table 24. Respiratory effects of vanadium pentoxide on experimental animals[a]

Reference	Species	Form	Concentration (mg/m^3)	Exposure	Pathological f
Sjöberg (1950)	rabbit	dust	205	7 h	conjunctivitis pulmonary oede pneumonia, ent liver, death
Sjöberg (1950)	rabbit	dust	20 - 40	1 h/day several months	chronic rhinit itis, emphysem asis, bronchop pyelonephritis
Gulko (1956)	rabbit	dust	10 - 30	continuous, acute	bronchitis, pn weight loss, b hoea
Roshchin (1963)	rat	dust, fume	80 - 700 10 - 70	continuous, acute	haemorrhagic i lungs, haemorr nal organs, pa piratory failu
Roshchin (1963)	rat	dust, fume	10 - 30 3 - 5	2 h/day, several months	haemorrhagic i lungs purulent pneumonia
Pazhynich (1966)	rat	fume	0.027	continuous 70 days	haemorrhagic i lungs, vascula haemorrhage in neys, and hear

[a] From: Waters (1977).

In acute studies on rats (Donryu strain) weighing 200 g, Kaku et al. (1971) administered vanadium (as ammonium vanadate) by gavage at a dose of 20 mg/kg body weight or injected it subcutaneously (doses of between 5 and 30 mg/kg body weight). There were dose-dependent reversible increases in the triglyceride concentrations in the liver and blood-serum, a decrease in the serum-cholesterol level, and increases in glutamate-oxalo-acetate transaminase and glutamate-pyruvate transaminase activity. After subcutaneous injection, there was a fall in cholesterol levels. The lowest values were reached 24 h after the injection; values then returned to normal. Dose-dependent increases were also observed in the concentrations of triglycerides in the liver and serum. Levels peaked 48 h after the injection and then gradually declined. When ammonium vandate solution equivalent to 1 mg vanadium/kg body weight was administered daily by subcutaneous injection for 30 days more marked changes in serum cholestrol were observed.

Korkhov (1965) injected 0.3 mg vanadyl sulfate/kg body weight subcutaneously in rabbits with experimental atherosclerosis and observed a lowering of the hypercholesterolaemia and inhibition of the rise in lecithin. Combined administration of vanadyl sulfate and phenylethylacetic acid lowered the aortic cholesterol level 3.5 times compared with controls. Korkhov (1965) also showed that cholesterol biosynthesis in liver tissue culture was inhibited by the addition of 10^{-4} vanadyl sulfate.

When 30 rabbits with experimental atherosclerosis were administered a mixture of trace elements (copper, cobalt, manganese, and zinc) in combination with cholesterol, Babenko & Vandzhura (1969) detected increases in the blood lipids and decreases in vanadium concentrations, compared with healthy control animals. The same results were noted following combined administration of copper and cobalt plus cholesterol at 0.2 g/kg. After administration of manganese, the decrease in the vanadium concentration was delayed; after administration of zinc, vanadium remained at the same level as in healthy animals. Vanadium concentrations in body tissues decreased as cholesterol levels increased, but manganese and zinc, when given together with cholesterol, helped maintain vanadium concentrations in the tissues of the body, the highest vanadium concentrations being found in the liver, aorta, and muscles.

In the studies by Novakova et al. (1981), daily oral administration to rabbits for 4 months of vanadium pentoxide and cholesterol (1st group: vanadium at 0.5 mg/kg body weight and cholesterol at 0.3 mg/kg body weight; 2nd group: vanadium at 1.5 mg/kg body weight and cholesterol at 0.5 mg/kg body weight) resulted in high levels of cholesterol in the blood and extensive atherosclerosis of the aorta. In the animals administered either cholesterol (0.5 mg/kg body weight) or vanadium (0.5 mg/kg body weight), hypercholesterolaemia was also observed, but the increase was less pronounced. Increases in levels of lipids, lipoproteins, and triglycerides were also observed. After one month of administration, cholesterol levels in treated animals were more than ten times those in the controls. At the end of the study (after the 4th month), the cholesterol levels in the treated animals were considerably higher than those in the controls.

The effects of vanadium on iron metabolism have not been fully elucidated. In some studies, a stimulative effect on haemoglobin and erythrocyte levels has been claimed. The results of studies by Myers & Beard (1931) suggested that vanadium chloride given at 0.6 mg/kg diet to rats, previously rendered anaemic, had a favourable effect on the haemoglobin level, and Kopylova (1971) obtained increases in the erythrocyte count and haemoglobin level in rabbits by subcutaneous administration of vanadyl sulfate (1 mg/kg body weight, daily, for 2 months). Trummert & Boehm (1957) observed an increase in the erythrocyte count following intravenous injection of vanadium gluconate (0.3 - 1.5 mg/kg body weight, daily, for 40 days), but the haemoglobin level was not significantly affected.

7.2.1 Mechanisms of action

Many of the metabolic effects observed can be explained by the biochemical effects of vanadium exposure in vivo and in vitro.

Roschin (1967a) presented the hypothesis that the mechanism of the initial step in the non-specific haematopoietic effect of vanadium and the subsequent anaemia was the inhibition of the redox system of hydrogen carriers. In response to the resulting hypoxia, there is increased haematopoiesis. Possibly vanadium interferes with tissue respiration at the stage of dehydrogenation effected by nicotinamide adenine dinucleotide (NAD). By inhibiting this coenzyme, vanadium interferes with the incorporation of iron in the porphyrin complexes and haemoglobin synthesis. The anti-vitamin C effect of vanadium and the consequent vitamin C deficiency also inhibits the utilization of iron for haemoglobin synthesis. Iron accumulates in the reticuloendothelial tissue.

It is known that vanadium also inhibits the activity of monoamine oxidase, which catalyses the conversion of serotonin to 5-hydroxyindoleacetic acid. In a study on rabbits exposed to vanadium pentoxide dust for 3 months, urine levels of 5-hydroxyindoleacetic acid fell to 33% below control values (Roschin, 1967a). It was suggested by the author that inhibition of monoamine oxidase might result in accumulation of serotonin in the central nervous system, leading to functional disturbances, such as bronchospasm, diarrhoea, and urinary incontinence. Elevated serotonin levels could also be responsible for the dystrophic and necrotic process in the kidneys and the high permeability of the blood vessels. A decrease in sulfhydryl groups in blood-proteins and a reduction in the cystine content of keratinized tissues might be due to an interaction between vanadium and an unspecified enzyme.

The catabolism of cystine and cysteine was increased by exposure to vanadium (Bergel et al., 1958). *In vitro,* pyridoxal 5-phosphate induced the catabolism of sulfhydryl amino acids in the presence of VO^{2+} (Anbar & Inbar, 1962). The authors suggested that the activation of pyridoxal phosphate by vanadyl ions was specific to elimination and strongly suggested a decrease in -SH groups in the organism. A reduction in cystine levels was observed in keratinized tissues (hair of rats fed vanadium compounds and the fingernails of vanadium workers) by Mountain et al. (1953, 1955). It was suggested that this effect was the result of decreased synthesis of cysteine and cystine and that metabolic processes depending on either of these amino acids may be depressed in the presence of vanadium.

According to Mahler & Cordes (1966), coenzyme A plays a central role in many biosynthetic and oxidative pathways. In the biosynthesis of coenzyme A, cysteine reacts with 4-phosphopantothenic acid in the presence of adenosine triphosphate (ATP) to form the intermediate 4'-phosphopantothenyl cystine, and Mascitelli-Coriandoli & Citterio (1959a,b) showed that treatment with sodium metavanadate reduced the content of coenzyme A in rat liver.

As coenzyme A is involved in biochemical pathways starting with acetate, these processes can also be affected by vanadium;

Curran (1954) showed that the synthesis of cholesterol from ^{14}C-acetate in rat liver was reduced in the presence of vanadium. Later studies indicated that one site of the inhibitory action of vanadium in the synthesis of cholesterol was at the level of the enzyme squalene synthetase, which catalyses the conversion of farnesyl pyrophosphate to squalene (Azarnoff & Curran, 1957; Azarnoff et al., 1961). In a study by Curran & Costello (1956), aortic cholesterol was mobilized more rapidly in vanadium-treated atherosclerotic rabbits than in controls. Cholesterol levels appear to be reduced by vanadium in young animals, including human beings, but not in older ones. It has been suggested, but not demonstrated, that a regulatory enzyme in the synthesis of cholesterol (acetoacetyl coenzyme A deacylase) is activated by vanadium in the former but inhibited in the latter.

Vanadium might reduce the synthesis of triglycerides and phospholipids, since acetyl coenzyme A is a precursor of fatty acids. However, the results of studies by Curran and colleagues showed that, while the levels of triglycerides decreased in the livers of rats given vanadium (Curran, 1954), serum-triglycerides levels in human beings increased following the ingestion of vanadium (Curran et al., 1959). Snyder & Cornatzer (1958) reported that the incorporation of labelled phosphate into rat liver phospholipids decreased following injection of vanadyl sulfate. This could have been due to the inhibition of phospho-lipid biosynthesis or to increased oxidative degradation, as originally suggested by Bernheim & Bernheim (1938, 1939). Using an isotope method with radioactive phosphorus as the indicator, Prokopenko (1961) observed a disturbance in the intensity of phosphorus exchange between organic acid-soluble compounds and inorganic phosphates in albino rats and mice with acute ammonium vanadate poisoning. No changes were found in the intensity of total metabolism and in liver tissue phosphate levels. After administration for 6 months in doses of 1 mg/kg body weight, phosphorylation processes in the organs and tissues were disturbed and the concentration of inorganic phosphorus in the blood and urine was increased.

Coenzyme A is also involved in the synthesis of coenzyme Q (ubiquinone) in the mitochondrial electron transport chain. Ubiquinone synthesis in isolated rat mitochondria was reduced by vanadium, but this effect was partially reversed when cysteine was given with vanadium. Addition of ATP and coenzyme A prevented the inhibition of ubiquinone synthesis (Aiyar & Sreenivasan, 1961).

It has been suggested that mitochondrial oxidative phosphorylation in liver homogenates *in vitro* is uncoupled by vanadium with a resulting depletion in ATP energy stores (Wright et al., 1960). In young chicks, the addition of ammonium metavanadate to the diet equivalent to 25 mg vanadium/kg body weight uncoupled oxidative phosphorylation in the liver mitochondria (Hathcock et al., 1966). These authors suggested that vanadate might replace the phosphate ion in ATP synthesis, and a high-energy vanadyl intermediate (vanadium X) or ADP-vanadium be formed and hydrolysed. The results of studies by DeMaster & Mitchell (1973) supported the theory of the mechanism involving the uncoupling of glyceraldehyde-3-phosphate

dehydrogenase by vanadium. It was also shown that the vanadium^{5+} oxyanion inhibited oxidative phosphorylation in intact rat liver mitochondria, but did not act as an uncoupler.

Vanadium salts inhibit the activity of succinic dehydrogenase, a key enzyme in the citric acid cycle and the electron transport system that is activated by sulfhydryl groups, and this would also reduce ATP synthesis (Aiyar & Sreenivasan, 1961). The inhibiting effects of vanadium on succinic dehydrogenase could involve a reduction in available -SH groups.

The oxidation of tryptamine by monoamine oxidase from guinea-pig liver and kidney was accelerated by 125% in the presence of vanadium (Perry et al., 1955, 1969); however, the results of studies by Lewis (1959c) on dogs injected with sodium metavanadate indicated that vanadium inhibited monoamine oxidase, because the urinary output of 5-hydroxyindoleacetic acid was reduced. The decreased output of 5-hydroxyindoleacetic acid, suggests the possibility of accumulation of serotonin, which was also reported by Roshchin (1967a).

When rats were administered daily injections of sodium metavanadate (1.25 - 2.5 mg/kg body weight), weight loss was correlated with accumulation of the metal in the liver (Johnson et al., 1974). The activities of the hepatic enzymes, xanthine oxidase and sulfite oxidase, which have molybdenum groups, and total liver concentrations of molybdenum were not affected by vanadium. It was concluded that vanadium toxicity in rats was not related to molybdenum utilization. Though vanadium was

administered in the pentavalent state, the rat livers had an electron paramagnetic resonance (EPR) spectrum characteristic of vanadium^{4+}. It was suggested that vanadium is in a protein-bound form in the livers of rats. Vanadium^{4+} was also found in the kidneys and, to a limited extent, in the lungs of rats injected with sodium metavanadate, but not in the hearts; it was considered that the ability of liver and kidney to reduce the vanadate by one electron might be related to a specific detoxification mechanism present in these organs. Johnson et al. (1974) and Minden & Rothe (1966) studied the effects of pentavalent vanadium salts on various enzyme systems in rat liver homogenates, rabbit blood-serum, and suspensions of erythrocytes and concluded that there was nothing to suggest that vanadium salts reacted directly with coenzymes (NAD and NADP, pyroxidal sulfate) or -SH groups.

The results of *in vitro* studies, conducted by Tolman et al. (1979), indicated that vanadium stimulated glucose oxidation and transport in adipocytes and glycogen synthesis in the liver and diaphragm, and inhibited hepatic gluconeogenesis and intestinal glucose transport. There is no evidence *in vivo* showing a role of vanadium in the regulation of glucose metabolism.

The intimate mechanism of interaction between vanadium and enzymes is not yet known. Experimentally observed disturbances of the cardiovascular system, changes in the concentration of -SH groups and cystine, disturbances in the metabolism of sulfur-containing, glycogen-forming, and keto-forming amino acids, and of the functioning of the liver and kidneys, of RNA

and DNA synthesis, and of cholesterol metabolism, indicate that vanadium possesses a broad spectrum of action in the body and that its toxic action is not analogous to that of any other metal (Roshchin, 1968).

7.3 Effects on the Nervous System

The Na^+K^+-ATPase in rat brain is inhibited by vanadium pentoxide, though not as strongly as that in kidney and heart (Nechay & Saunders, 1978). Svoboda et al. (1984) showed that the brain microsomal N^+K^+-ATPase in rat is equally inhibited by vanadate (VO^{3-}) or the vanadyl ion (VO^{+2}).

In a short-term exposure study, rats received single intraperitoneal injections of sodium metavanadate equal to 20% of the LD_{50} (1 mg vanadium/kg body weight). The level of noradrenaline decreased and those of dopamine and 5-hydroxy-tryptamine increased. A long-term study involved the oral administration of sodium metavanadate (3 mg vanadium/kg body weight). The findings were similar to, but more pronounced than, those in the short-term study (Witkowska & Brzezinski, 1979).

When adult male CD1 mice were treated with vanadate in the drinking-water for 30 days, there was a dose-related decrease in norepinephrine levels in the hypothalamus. Dopamine levels also decreased significantly, but 5-hydroxytryptamine levels were not affected. Levels of dopamine in the corpus striatum were unchanged and there were only marginal effects on the amines in the other brain regions. It is suggested that vanadium has a selective effect on adrenergic pathways (Sharma et al., 1986).

Several inhibitors of Na^+K^+-ATPase, such as ouabain, have been reported to block DNA and protein synthesis in cell cultures (Kaplan, 1978). It has also been shown that vanadate inhibits protein synthesis in neuroblastoma cells and in the brain homogenates of rats fed sodium monovanadate (125 mg/litre) *ad libitum* for 30 or 60 days (Montero et al., 1981).

Neurophysiological effects have been reported following acute exposure (oral and sc injection) of dogs and rabbits to vanadium oxides and salts (V_2O_3, V_2O_5, VCl_3, NH_4VO_3) (Roshchin, 1967a). These include disturbances of the central nervous system (impaired conditioned reflexes and neuromuscular excitability).

In studies by Seljankina (1961), solutions of vanadium pentoxide or ammonium vanadate were administered orally to rats or mice in doses of 0.005 - 1 mg vanadium/kg body weight per day for periods ranging from 21 days at the higher levels to 6 months at the lower levels. A dose of 0.05 mg vanadium/kg body weight was found to be the threshold dose for functional disturbances in conditioned reflex activity in both mice and rats; a dose of 0.005 mg vanadium/kg body weight did not produce any adverse effects.

In a study by Pazhynich (1966), albino rats underwent continuous inhalation exposure to condensation aerosols of vanadium pentoxide at levels of 0.002 mg/m^3 and 0.027 mg/m^3. Animals in

both treated and control groups showed normal weight gain. After 30 days, the motor chronaxy of the extensor muscles of the tibia in the group exposed to 0.027 mg/m^3 decreased by an average of 0.8 μs ($P < 0.01$), and the chronaxy of the corresponding flexor muscles increased by an average of 4 μs ($P < 0.001$). Thus, the chronaxy ratio of antagonistic muscles fell from 1.5 at the beginning of the studies to 1.0 on day 20 ($P < 0.02$), and 0.5 on day 30 ($P < 0.01$). The decrease continued until a level of about 0.25 was reached. About 18 days after cessation of exposure on the 70th day, the chronaxy ratio returned to normal (1.5). Changes in motor chronaxy were not observed in rats exposed at 0.002 mg/m^3 or in the controls.

In a second study, albino rats were exposed continuously to vanadium pentoxide at 0.006 ± 0.00056 mg/m^3 for 40 days. No changes were observed in the chronaxy of antagonistic muscles of the tibia in exposed animals, compared with the controls, during the first month of exposure. However, after 30 days, there was a statistically significant decrease in chronaxy ratio. When animals were given only water and no food for 3.5 days, during the sixth week of exposure, chronaxy ratios decreased to 0.92, compared with 1.5 in the controls.

7.4 Effects on the Respiratory System

Studies on respiratory exposure to vanadium pentoxide are summarized in Table 23 (section 7.1).

Sjöberg (1950) exposed rabbits to vanadium pentoxide dust particles, nearly all of which were smaller than 10 μm in diameter at concentrations of 77, 109, 205, or 525 mg/m^3 for periods of 7 h, 4 h, 7 h, or 1 h, respectively. Death occurred only in the 205 mg V_2O_5/m^3 (7 h) group (equivalent to 115 mg vanadium/m^3). There was marked tracheitis accompanied by pulmonary oedema and bronchopneumonia. Conjunctivitis, enteritis, and fatty infiltration of the liver were also observed.

In further studies by the same author, rabbits were exposed to 20 - 40 mg V_2O_5/m^3 (equivalent to 11 - 22 mg vanadium/m^3) intermittently for 1 h each day for several months. At autopsy, pathological changes observed included chronic rhinitis and tracheitis, emphysema, patches of lung atelectasis, broncho-pneumonia and, in some cases, pyelonephritis. Vanadium was detected in ashed lung, liver, and kidney, but not in the intestines. Changes of a fibrotic nature and specific chronic lesions were not observed in the lungs, and there was no visible accumulation of particles. These findings, plus the fact that vanadium was present in the liver and kidney, were considered evidence of rapid clearance and/or absorption from the lung.

Continuous inhalation exposure of rabbits to 10 - 30 mg V_2O_5/m^3 (5.6 - 16.8 mg vanadium/m^3) caused bronchitis, pneumonia, loss of weight, and bloody diarrhoea (Gulko, 1956).

In studies by Roshchin (1967b, 1968) described in section 7.2, acute inhalation toxicity in albino rats was characterized by irritation of the respiratory mucosa and nasal discharge that sometimes contained blood. Animals breathed with difficulty and

there were crepitations. The animals behaved passively, refusing to eat, and lost weight. In cases of severe poisoning, diarrhoea, paralysis of the hind limbs, and respiratory failure were followed by death. Pulmonary abscesses were frequently seen in animals that recovered. Animals that died or were killed at various times after exposure, showed severe congestion, particularly in the capillaries, and small haemorrhages were observed in all internal organs. Signs of increased intracranial pressure, and fatty degeneration of the liver and kidneys were also seen. In the lungs, there was capillary congestion together with tiny haemorrhages, perivascular and focal oedema, bronchitis, and focal interstitial pneumonia. The bronchitis and bronchopneumonia were often purulent, and the small bronchi were constricted. There was a relationship between the severity of the pathological changes and the vanadium concentration in the air. In cases of slight toxicity, pathological changes were mainly confined to the lungs.

Pathological changes were also seen in the lungs when rats were exposed intermittently to a condensation aerosol of vanadium pentoxide at 3 - 5 mg/m^3 for 2 h, every other day, for 3 months, or to a dispersion aerosol of V_2O_5 at 10 - 30 mg/m^3 for 4 months. Blood vessels were engorged and the endothelium was swollen; capillary congestion, perivascular oedema, lymphostasis, and small haemorrhages indicated altered vascular permeability and disturbances in the circulation of the pulmonary blood and lymph. Occasionally, foci of oedema and desquamative bronchitis were observed and small bronchi were often constricted. Lymphocytes and histiocytes had infiltrated interstitial tissue. Connective tissue proliferation was sometimes seen in the zone of lymphocytic infiltration. Purulent bronchitis or pneumonia occurred in some animals, and occasionally lung abscesses developed.

Roshchin (1967a) observed similar effects with vanadium trioxide and vanadium trichloride. As vanadium trichloride was more soluble, more marked histopathological effects were seen in internal organs. Pentavalent compounds of vanadium were 3 - 5 times more toxic (in terms of median lethal concentration) than trivalent compounds. Although dispersion aerosols of vanadium metal, vanadium carbide, and ferrovanadium were not highly toxic, long-term exposure at high concentrations resulted in many of the signs and symptoms produced by vanadium pentoxide.

In studies by Pazhynich (1966) (section 7.2), histopathological changes observed in rats following high-level inhalation exposure included marked lung congestion, focal lung haemorrhages, and extensive bronchitis.

Effects on the lung were observed in albino rats exposed by inhalation for 2 weeks to uncoated bismuth orthovanadate dust (0.11 mg/litre, 1.2 mg/litre), silica-coated bismuth orthovanadate (0.15 mg/litre, 1.3 mg/litre), or silica-coated titanium dioxide (1.19 mg/litre). In rats sacrificed at the end of the 2-week exposure, there was a dose-related macrophage (dust cell) response to both forms of bismuth orthovanadate. Three months after exposure, the bismuth orthovanadate rats had alveolar proteinosis, foamy macrophages with cholesterol clefts,

and hyperplastic type II pneumocytes. Six months after exposure, these changes were more marked with cholesterol granulomas and degeneration of foamy macrophages. In rats sacrificed after 1 year, the pulmonary lesions were reduced, but alveolar proteinosis and cholesterol granulomas persisted. Initially, similar changes were observed in rats exposed to the silica-coated titanium dioxide, but recovery was obvious at 6 months and, at 1 year, the lungs were almost normal with only a few remaining macrophage (dust cell) aggregates (Lee & Gillies, 1986).

The respiratory and related histopathological effects of vanadium exposure in experimental animals were marked irritation of the respiratory mucosa; vascular injury resulting in capillary stasis, perivascular oedema, and small haemorrhages; and an asthmatic-type bronchitis and expiratory difficulty on acute exposure (Roschin, 1967b).

In adult male cynomolgus monkeys exposed by inhalation to vanadium pentoxide dust concentrations of 0.5 mg/m^3 or 5 mg/m^3 at weekly intervals, significant central and peripheral airflow restriction was measured one day after each exposure. There were also significant increases in respiratory cell counts obtained by bronchoalveolar lavage. The increased cell count was due to a marked increase in the number (absolute and relative percentage) of polymorphonuclear leukocytes, indicating pulmonary inflammatory changes (Knecht et al., 1985).

In the respiratory tract of experimental animals, the main differences between the acute and chronic effects of vanadium are the development, after prolonged exposure, of chronic inflammation in the bronchi and a greater tendency to septic bronchopneumonia. Atelectasis, interstitial infiltration and proliferation, and emphysema also occur.

Macrophages are engaged in a variety of pulmonary defence mechanisms. Theoretically, effects of vanadium on these cells may explain some of the observations on vanadium toxicity on the respiratory system. In in vitro studies, Waters et al. (1974) demonstrated a 50% reduction in the viability of cultured rabbit macrophages after exposure to 13 mg vanadium/litre (as vanadium pentoxide) for 20 h. Short-term exposure (2 h) to vanadium pentoxide at a dose of 7 mg vanadium/litre also reduced the viability of mouse pulmonary alveolar macrophages to 87%. In another study, the phagocytic index was reduced to 71% (Fisher et al., 1978). The incubation of bovine alveolar macrophages with ammonium metavanadate (NH_4VO_3) at 0.5 or 1 mg vanadium/litre, for 4 h, reduced viability to 95 and 85%, respectively. After 8 h incubation, viability was reduced by 24 and 38%, respectively, and, after 16 h, no viable cells remained. Low levels of vanadium (0.01, 0.1 mg vanadium/litre) stimulated the phagocytic activity of macrophages, whereas a striking decrease in phagocytic activity was noted with 0.5 and 1 mg/litre at 8 h, though, initially, there was stimulation of activity. Doses of 0.01 and 0.1 mg/litre did not affect viability (Wei & Misra, 1982).

7.5 Effects on the Cardiovascular System

Severe exposure of animals to vanadium oxides and salts

produced cardiovascular changes (occurrence of arrythmias and extrasystole, prolongation of the Q-RST interval, and decrease in the height of the P and T waves of the EKG) (Roshchin, 1967a).

Intense vasoconstriction has been reported in the spleen, kidney, and intestines following intravenous injections of sub-lethal doses of sodium ortho- and metavanadate (Hudson, 1964).

Intravenous injection of sodium metavanadate at 2.5 mg/kg in dogs provoked an increased amplitude of T-waves in the electro-cardiogram followed by depression of S-T segments (Lewis, 1959c). Perivascular swelling, as well as fatty changes in the myocardium, were observed by Roshchin (1968) following long-term inhalation exposure of rats and rabbits to vanadium pentoxide, trioxide, and chloride (10 - 70 mg/m^3, 2 h/day, 9 - 12 months).

Vanadium sulfate (500 mg/kg diet, 6 weeks) mobilized excess arterial cholesterol in rabbits previously maintained on a cholesterol-rich diet (Curran & Costello, 1956).

Feeding rats sodium orthovanadate at 100 or 200 mg/kg body weight (added to normal rat chow) for up to 56 weeks resulted in a gradual increase in systolic blood pressure. The effect was unrelated to water intake, urine output, or urinary-sodium excretion. The increased pressure was sustained in a dose-related manner and was positively correlated with plasma levels of vanadium that ranged from 0.04 to 0.27 mg/litre (Steffen et al., 1981). Similar increases in mean arterial blood pressure have been reported in both conscious (Day et al., 1980) and anaesthetized rats (Hatfield & Churchill, 1981).

7.6 Effects on the Kidney

In earlier studies, glomerular hyperaemia and necrosis of convoluted tubules were reported to be related to acute vanadium exposure (Hudson, 1964). Nephrotoxicity, manifested as albuminuria, was reported after intravenous injection of sodium metavanadate at 2.5 - 5 mg/kg body weight in male dogs by Lewis (1959c). Inhalation of 10 - 70 mg vanadium chloride/m^3, for 2 h daily, for 9 - 12 months, was followed by fatty changes in the kidney of the rat and rabbit (Roshchin, 1968). In an inhalation study on rats exposed continuously to vanadium pentoxide condensation aerosols at concentrations of 0.002 and 0.027 mg/m^3 for 70 days, Pazhynich (1966) reported granular degeneration of the epithelial cells of the convoluted tubules, with areas of necrosis. Acute tubular necrosis followed subcutaneous injection of NH_4VO_3-solutions in 0.1 mol/litre tris-HCl-NaCl buffers in albino mice (20 mg vanadium/kg body weight). The mortality rate was higher at a pH of 7.8 (68%) than at pH 6.1 (20%) (Wei et al., 1982).

There are distinct species differences with regard to the renal effects of vanadate (Grantham, 1980; Phillips et al. 1983; Nechay, 1984). Vanadate has both diuretic and natriuretic effects on the rat kidney (Balfour et al., 1978; Day et al. 1980; Kumar & Corder, 1980; Hatfield & Churchill, 1981; Roman et al., 1981), but not on that of the dog (Inciarte et al., 1980;

Lopez Novoa et al., 1982a,b) or the cat (Larsen et al., 1979). In the rat, the tubular effect is independent of changes in glomercular filtration rate, whereas the tubular effect in the cat is either absent or masked by pronounced renal vasoconstriction and anuria (Larsen et al., 1979; Larsen & Thomsen, 1980). Vanadate has also been reported to increase the urinary excretion of calcium, phosphate, bicarbonate, and chloride in the rat kidney (Kumar & Corder, 1980).

7.7 Effects on the Immune System

Exposure of mice to vanadium in drinking-water resulted in a dose-related, but not statistically-significant, decrease in antibody-forming cells in the spleens of mice challenged with sheep erythrocytes; serum immunoglobulins were not affected. Splenic lymphocytes obtained at 1, 4, 8, and 13 weeks from male Swiss-Webster mice treated with 1, 10, or 50 mg vanadium/litre drinking-water showed increased DNA synthesis *in vitro* (Sharma et al., 1981). In female B6C3F1 mice given ammonium metavanadate ip at doses of 2.5, 5, or 10 mg/kg body weight, every 3 days, for 3, 6, or 9 weeks, there was a dose-related increase in resistance to *Escherichia coli* endotoxin lethality up to 6 weeks and a dose-related decrease in resistance to Listeria lethality. Peritoneal macrophage activity also decreased in a dose-related manner, but without any effects on viability. The rosetting capability of splenic lymphocytes was increased. There was enlargement of the liver and spleen with enhanced formation of splenic mega-karyocytes and red blood cell percursors. The authors concluded that vanadium may affect the normal functioning of the immune system (Cohen et al., 1986).

7.8 Reproduction, Embryotoxicity, and Teratogenicity

7.8.1 Reproduction and embryotoxicity

Roshchin at al. (1980) studied the gonado- and embryotoxic effects of 0.85 mg metavanadate/kg body weight (1/20 LD_{50}), administered subcutaneously to albino rats. Vanadium administered to pregnant rats on days 21 - 22 of pregnancy accumulated in the placenta but was not reported to penetrate the placental barrier and reach the fetus. During the period of lactation, vanadium was found in the mammary glands (0.14% of administered dose/g tissue) and excreted with the milk. In newborn rats, the uptake of vanadium was in the range of 0.018 - 0.032% of the original administered dose to the lactating dams per g neonate. Impairment of spermatogenesis was manifested as a 10 - 33% decrease in the mobility of spermatozoa, a decrease in osmotic resistance of 7.9 - 11.4% and a 31% rise in the number of dead spermatozoa. There were morphological changes in spermatozoa and desquamation of the spermatogenic epithelium in the seminal tubuli. The impairment of spermatogenesis affected the reproduction of animals, resulting in pre-implantation deaths of embryos. Gonadotoxic effects were suggested by the absence of fertilization of female rats by male rats exposed daily to vanadium at 0.85 mg/kg body weight. In other studies (Hackett & Kelman, 1983) in pregnant rats vanadium tended to localize initially in the placenta and then to preferentially concentrate in the membranes rather than in the fetus.

The administration of similar doses of vanadium to female

rats on the 4th day of pregnancy increased the mortality of embryos as a result of pre-implantation deaths; the number of fetuses in each female rat was only half that in the untreated animals. These effects were observed in the absence of general toxicity in the experimental animals.

In vitro, orthovanadate (0.2 - 2 mmol) inhibited luteinizing hormone-induced cyclic adenosine monophosphate (cAMP) in isolated corpora lutea from pseudopregnant rats. When added simultaneously with luteinizing hormone, inhibition occurred within 25 min, but not when the *corpora lutea* had been pretreated with luteinizing hormone for 60 min. A decrease was also observed when *corpora lutea* were exposed to vanadate in the presence of 3-isobutyl-1-methylxanthene (0.5 mmol), a phosphodiesterase inhibitor. Cyclic adenosine monophosphate was also inhibited by vanadate in *copora lutea* incubated in a calcium-depleted medium. Vanadyl sulfate (0.4, 2 mmol) was as effective as vanadate in inhibiting luteinizing hormone-induced cyclic adenosine monophosphate accumulation (Lahav et al., 1986).

7.8.2 Teratogenicity

Carlton et al. (1982) injected 80 mature Syrian golden hamsters ip with ammonium vanadate at 0, 0.47, 1.88, or 3.75 mg/kg body weight. Injections were carried out on days 5 - 10 of gestation. A significant increase in skeletal anomalies was observed in all groups exposed to vanadate compared with control animals. A significant increase in deaths was registered in the 1.88 mg/kg group. There was no dose-response relationship as regards anomalies.

Pregnant NMRI albino mice were injected intravenously with 1 mmol vanadium pentoxide dissolved in distilled water on day 3 or day 8 of pregnancy (day 1 = finding of vaginal plug). Control groups were given 0.1 ml physiological saline on the same days. Mice were killed on day 17, the uterine horns examined for resorbed embryos, and the fetuses were removed for detailed examination. Vanadium pentoxide did not produce any effects in implantation, and fetuses from the day 3-treated and control groups did not show any differences in litter size, fetal weight, or external and internal morphology. The fetuses from the day 8-treated group showed a statistically significant high frequency (71%) of delayed ossification (supraoccipital bone, sternum, metatarsals, and caudal vertebrae), and broken spinal cord occurred in a few fetuses (Wide, 1984).

Vanadium pentoxide was administered subcutaneously to pregnant rats (strain unspecified) at doses of 0.5, 1, or 4 mg/kg body weight for 10 days, from day 7 to day 16 of gestation. The incidences of resorbed and dead fetuses in the 1 and 4 mg/kg groups were 17% and 27.2%, respectively. These were significantly higher than those found in the controls (3.5%). In the 4 mg/kg group, 52.38% of fetuses showed wavy ribs. In a separate study, pregnant rats were given an aqueous solution of V_2O_5 by ip injection at concentrations of 0.3, 1, or 3 mg/kg body weight. This induced a higher level of resorbed and dead fetuses than oral administration. Both ip injection of 0.3 mg/kg and oral administration of 9 mg/kg induced an array of skeletal anomalies, namely wavy ribs, supernumerary ribs, and fused sternebrae and vertebrae (Sun, ed., 1987). Though

tentative, these results suggest that vanadium may have the potential to induce teratogenicity in a mammalian system.

7.9 Mutagenicity and Related End-Points

There are few studies on the mutagenicity and carcinogenicity of vanadium compounds. Mutagens in the air can be divided into two groups: a non-polar extract rich in polycyclic aromatic hydrocarbons (PAHs) and other promutagens, and a polar extract containing direct acting mutagens, i.e., not requiring microsomal activation (Madsen et al., 1982). The non-polar fraction was strongly influenced by automobile exhaust products, whereas the polar was more attributable to secondary emissions transformed by atmospheric reactions, and to primary emissions from stationary sources. The role of PAHs in the overall mutagenicity was estimated to be modest; thus, the importance of other substances increases. Vanadium was found at all sample sites and is a well-known constituent of, for instance, coal fly ash (section 3.4.2).

Vanadium^{5+} has been shown both to inhibit or enhance DNA synthesis *in vitro* , depending on the concentration in the media (Hori & Oka, 1980; Carpenter, 1981; Jackson & Linskens, 1982; Smith, 1983).

In a DNA synthesis inhibition assay in male mice, vanadium pentoxide suspended in 3% starch solution was administered orally at doses of 14.6, 29.2, or 58.4 mg/kg body weight. The animals were killed 24 h after dosing; 3 h before sacrifice, 1 μCi ^{3}H-thymidine/g body weight was administered ip. Incorporation of ^{3}H-thymidine in the testes, spleen, liver, and blood was measured in a liquid scintillation spectrometer. There were no significant differences between the experimental groups and the solvent control group (Sun, ed., 1987).

In a study using FADU (Fluorescence Analysis of DNA Unwinding), vanadyl chloride at a concentration of 5 x 10^{-5} mol failed to induce DNA damage (strand breaks) in human peripheral white blood cells (McLean et al., 1982).

Kanematsu et al. (1980) carried out rec assays on 127 metal compounds with Bacillus subtilis to test their DNA-damaging capacity. Mild positive results were noted for three vanadium compounds ($VOCl_2$, V_2O_5, NH_4VO_3).

A lack of induction of spot mutations in *Escherichia coli* and in *Salmonella typhimurium* was demonstrated by Kanematsu & Kada (1978) and Kada et al. (1980). Similar results were obtained by Si Rongshan et al. (1982) with *E. coli* . However, ammonium metavanadate was found to be mutagenic in *S. typhimurium* TA1535 in a modified plate incorporation assay and in the fluctuation test with TA100 (Arlauskas et al., 1985). In a recent study, Sun, ed. (1987) demonstrated the induction of reverse mutations by vanadium pentoxide with E. coli WP2, WP2uvrA, and Cm-981, but no frameshift mutations with strains ND-160 and MR102. Vanadium pentoxide showed negative results with *S. typhimurium* strains TA1535, TA1537, TA98, and TA100. Thus, the results of mutagenicity studies of vanadium with bacterial assays are conflicting, and no firm conclusions can be

drawn.

In a micronucleus test, vanadium pentoxide was administered to two strains of mice (615 and Kunming albino) by ip injection at doses of 6.4, 2.13, or 0.17 mg/kg body weight for 5 consecutive days; cyclophosphamide was used as a positive control (Sun, ed., 1987). Significant levels of induced micronuclei in both strains were observed. Both subcutaneous injection of vanadium pentoxide solution (0.25, 1, or 4 mg/kg) and inhalation of vanadium pentoxide dust (0.5, 2, or 8 mg/m^3) also induced micronuclei in mice strain 615. However, negative results were obtained following oral administration of a 3% starch suspension of vanadium pentoxide at doses of 1.44, 2.83, 5.65, or 11.3 mg/kg body weight, daily, for 6 weeks, to Kunming albino mice (Sun, ed., 1987).

In an *in vitro* study on human peripheral lymphocyte cultures with vanadium pentoxide concentrations of 0.047, 0.47, or 4.7 moles (mitomycin c was used as positive control), no increases in the frequency of sister chromatid exchange were observed (Sun, ed., 1987).

In a dominant-lethal mutation assay, vanadium pentoxide (0.2, 1, or 4 mg/kg body weight) was administered daily by subcutaneous injection to 5 groups of male mice, aged 5 - 6 weeks at the start of the study, for 3 months, following which they were mated with females. Ethylmethanesulfonate and distilled water were used as positive and negative controls, respectively. The females were killed 17 days after conception and the numbers of fetuses and resorptions recorded. The results were considered negative for the induction of dominant-lethal mutations (Sun, ed., 1987).

7.10 Carcinogenicity

In a study on 13 metallic compounds, intraperitoneal injections of vanadium^{3+} 2.4-pentanedione at doses of 24, 60, or 120 mg/kg body weight did not significantly increase the incidence of lung adenomas in mice (Stoner et al., 1976).

In life-span studies, the incidence of tumours in mice given vanadyl ions (as the sulfate) at 5 µg/litre drinking-water was similar to that in control animals (Kanisawa & Schroeder, 1967; Schroeder et al., 1970; Schroeder & Mitchener, 1975).

In rats, the induction of mammary carcinogenesis by 1-methyl-1-nitrosurea was blocked by feeding a purified diet supplemented with 25 mg vanadyl^{4+} sulfate/kg during the post-initiation stages of the neoplastic process. Both cancer incidence and the average number of cancers per rat were reduced by the vanadium^{4+} diet without inhibiting the overall growth of the animals (Thompson et al., 1984). It has also been shown that metallocene dichlorides, $(C_2H_5)_2MCl_2$ (where M = titanium, vanadium, molybdenum, or niobium), exhibit cancerostatic activity against the Erlich ascites tumour system in mice, and that treatment with such substances cured the tumour (Köpf-Maier et al., 1980). Vanadocene dichloride was reported to have a

chemotherapeutic activity similar to that of cis-dichlordiamine platinum (II) when used against liver tumours in mice (Köpf-Maier & Köpf, 1979). The mechanism of the preventive effect of vanadium is not clear. Modulation of one or more aspects of the DNA metabolism could account for these results.

The effects of ammonium vanadate on the development of large bowel neoplasms in mice treated with 1,2-dimethylhydrazine (DMH) were studied by Kingsnorth et al. (1986). Mice were treated with DMH (20 mg/kg body weight per week) for 20 weeks. Ammonium vanadate was given in the drinking-water (10 or 20 mg/litre) to groups of mice during the study. At 30 weeks, the colons of DMH-treated mice (not receiving ammonium vanadate) showed increases in RNA content (+14%) and DNA content (+18%) and deeper crypts (+33%). In the mice treated with DMH and receiving ammonium vanadate at 10 or 20 mg/litre, the RNA content was decreased by 11%. Although thymidine incorporation was increased, ammonium vanadate did not have any effects on the incidence or type of tumour induced by DMH (Kingsnorth et al., 1986).

In a long-term study in which the carcinogenic activity of various materials was studied using intrabronchial pellet implantation in the lower left bronchus of rats, vanadium solids produced chronic inflammatory changes in 44/100 rats, bronchial inflammation in 50/100, squamous metaplasia in 10/100, and one bronchial carcinoma in a male rat after 645 days. These results were not significant for carcinogenicity (Levy et al., 1986).

8. EFFECTS ON MAN

8.1 Therapeutic Exposure and Controlled Studies

8.1.1 Therapeutic exposure

In the past, vanadium compounds were prescribed as therapeutic agents for anaemia, chlorosis, tuberculosis, and diabetes. They were also used as an antiseptic, a spirochetocide, and a tonic. For example, sodium metavanadate was given therapeutically by mouth in doses of 1 - 8 mg, and sodium tartrate was injected intramuscularly at levels as high as 150 mg. Due to poor absorption from the gastrointestinal tract, the metal is not very toxic for human beings when ingested, but, if introduced directly into the circulation in a soluble form, Hudson (1964) estimated that the lethal dose for a 70-kg person would be only 30 mg V_2O_5 (0.42 mg V_2O_5/kg body weight).

8.1.2 Controlled studies

8.1.2.1 Effects on metabolism

Vanadium has been administered under controlled conditions to study its effects on blood-cholesterol levels. Curran et al. (1959) conducted a clinical study in which 5 healthy adult male volunteers were fed soluble diammonium oxytartarovanadate at 150 - 200 mg/day (21 - 30 mg vanadium/day) for 6 weeks. At the end of the period, plasma-cholesterol was significantly reduced.

Lewis (1959a) compared age-matched groups of 32 vanadium

workers with 45 controls, all over 45 years of age. Vanadium workers exposed for at least 6 months excreted greater amounts of vanadium and exhibited slightly lower serum-cholesterol levels than the controls. Mean cholesterol values for the 2 reference groups (representing 2 geographical areas) were 2309 and 2267 mg/litre. Mean levels for vanadium workers from corresponding areas were lower at 2049 and 2067 mg/litre ($P < 0.05$), respectively.

A clinical study by Somerville & Davies (1962) on 12 patients (9 of whom were hypercholesterolaemic) given diammonium vanadotartrate orally for 6 months (25 mg 3 times daily for 2 weeks, increased to 125 mg daily in 10 patients) did not show any significant changes in serum-cholesterol levels over 5.5 months. The mean pretreatment control level of serum-cholesterol was 4110 mg/litre, and the mean age was 49.2 years. The study is not comparable with that of Curran et al. (1959), as the patients were hypercholesterolaemic and older. Dimond et al. (1963) observed temporary drops (not statistically significant) in cholesterol levels in 2 out of 6 patients given ammonium vanadyl tartrate for several weeks at levels of between 50 and 100 mg/day. No statistically significant changes were observed in blood-lipids, phospholipids, triglycerides, 17-ketosteroids, or 17-hydroxycorticosteroids. Two patients complained of fatigue and lethargy while they were taking vanadium. All complained of cramps and loosened stools, and all developed green tongue. Schroeder et al. (1963) reporting findings similar to those of Dimond et al. (1963) considered that the slight effects of vanadium on serum-cholesterol were pharmacological rather than caused by correction of a physiological deficiency. They further pointed out that dietary regimens based on the consumption of unsaturated fats, which reduce plasma-cholesterol in human beings, are associated with the intake of 1 - 4 mg vanadium/day and that the feeding of vanadium-poor saturated fats raises cholesterol.

Studies have been undertaken on the effects of vanadium on human dental caries. Belehova (1969) studied 583 school children ranging in age from 7 to 11 years. The subjects were divided into 4 groups. Children in Group I received fluoride twice a year, those in Group II received a local application of a 50% paste of an ammonium salt of vanadium and glycerol, Group III received both fluoride and vanadium, and Group IV acted as the control. The incidence of caries was 11% in Group III, 15.4% in Group II, 29.7% in Group I, and 43% in the control group. Belehova concluded that the lower incidence of caries in subjects receiving vanadium suggested a possible prophylactic action. However, other studies (Hein & Wisotzky, 1955; Muhler, 1957; Hadjimarkos, 1966, 1968; McLundie et al., 1968) failed to demonstrate a clearly beneficial effect with regard to dental caries in human beings.

Data on the effects of vanadium on the haematopoiesis are inconsistent. Lewis (1959a) did not observe any effects of exposure to vanadium on haematocrit levels in 32 vanadium workers compared with 45 controls matched for age. A beneficial effect of low-level vanadium administration on nutritional anaemia has been suggested (Beard et al., 1931; Myers & Beard 1931; Hadjimarkos, 1966; Kopylova, 1971). However, the effects

of vanadium on iron metabolism have not been fully assessed (Vouk, 1979).

The administration of *w*-methylpantothenic acid, an antimetabolite of pantothenic acid, to human beings resulted in a syndrome consisting of postural hypotension, dizziness, tachycardia, fatigue, drowsiness, epigastric distress, anorexia, numbness and tingling of the hands and feet, and hyperactive deep reflexes. It is not known whether these symptoms are the result of an induced deficiency of pantothenic acid or are toxic effects of the anti-metabolite. However, the symptoms resemble those resulting from exposure to high concentrations of vanadium. The common denominator in both cases may be a reduction in hepatic coenzyme A levels (Waters, 1977).

8.1.2.2 Effects on the respiratory system

Zenz & Berg (1967) studied the effects of vanadium inhalation in 9 healthy volunteers aged 27 - 44 years, for whom baseline lung function data were available. Two volunteers, exposed to vanadium pentoxide dust at 1 mg/m^3 for 8 h, developed sporadic coughing after 5 h and a frequent cough after nearly 7 h. Coughing lasted 8 days, but lung sounds remained clear and there were no other signs of irritation. Lung function tests, complete blood counts, urinalyses, and nasal smears were normal up to 3 weeks. Three weeks later, the same 2 volunteers were accidently exposed for 5 min to a "heavy cloud" of vanadium pentoxide dust. A productive cough developed within 16 h, and, within 24 h, rales and expiratory rhonchi developed throughout the lung, but pulmonary function remained normal. Isoproterenol (1:2000) relieved the symptoms for about 1 h, but coughing then resumed and continued for 7 days. There were no other symptoms. Eosinophils were not present in the nasal mucous.

Exposure of 5 volunteers to a lower concentration (0.2 mg/m^3, 98% of particle size 5 μm) had similar effects, though the symptoms took longer to develop, i.e., after 20 h. Coughing, without other systemic effects, persisted for 7 - 10 days. Pulmonary function tests and differential white blood counts remained normal. The vanadium concentration in the urine was highest (0.13 mg/litre) on the third day, with none detectable after 7 days. The maximal faecal-vanadium level was 3 mg/kg, with none detectable after 14 days. Exposure to a concentration of 0.1 mg/m^3 for 8 h did not produce any coughing in 2 subjects not previously exposed. However, an increase in the production of mucous, 24 h later, indicated some respiratory irritation. Then there was slight coughing, which became more severe after 48 h, subsided after 72 h, and disappeared after 96 h. Pulmonary function tests and differential white blood counts remained normal.

Pazhynich (1967) studied the irritant effects of vanadium pentoxide condensation aerosol on 11 volunteers. At a concentration of 0.4 mg/m^3, all reported a tickling or itching sensation and a feeling of dryness in the region of the root of the tongue, the posterior wall of the pharynx, and the fauces, as well as a slight prickling sensation in the nose and posterior pharyngeal wall. These symptoms were easily tolerated.

A concentration of 0.16 mg/m^3 caused mild signs of irritation in only 5 volunteers, and a concentration of 0.08 mg/m^3 was not noticed by any volunteer. It was concluded that the mean perceptible concentration for human beings is 0.27 mg/m^3 and that 0.16 mg/m^3 is imperceptible.

8.2 Clinical Studies

The clinical picture of poisoning shows the broad spectrum of toxic effects of vanadium. The lesions observed affect the respiratory system, circulatory system, central nervous system, digestive organs, kidneys, and skin. Poisoning can be divided into acute and chronic forms.

8.2.1 Acute toxicity

Acute toxicity is characterized by a latent period, which depends on the concentration of vanadium, the individual sensitivity of the subject, and the properties of the specific vanadium compound. The more soluble salts of vanadium pentoxide have a more rapid action than the vanadium oxides. Chemically-pure vanadium pentoxide acts more rapidly than the technical grade. A condensation aerosol of vanadium pentoxide is more toxic than a disintegration aerosol (Roshchin, 1964). Vanadium chloride is toxic more rapidly than other compounds.

Roshchin (1968) subdivided acute vanadium effects into "mild", "moderate", and "severe" forms. The clinical features of mild toxicity include rhinitis with a profuse and often bloody discharge, sneezing, and an itching and burning sensation in the throat. The rhinitis may be followed by the development of a dry cough with expectoration of small amounts of viscid sputum, general weakness, and exhaustion. A sub-normal temperature may be present; in other cases, the temperature may be high or normal. The patient is afebrile in the absence of pneumonic disease (Sjöberg, 1950). Conjunctivitis is frequently observed. The symptoms and course of mild toxicity resemble an upper respiratory tract infection. Other symptoms include diarrhoea due to intensified intestinal peristalsis. The symptoms disappear from 2 - 5 days after cessation of contact with the dust.

In moderate toxicity, in addition to conjunctivitis and irritation of the upper respiratory tract, there is bronchitis with expiratory dyspnoea and bronchospasm. There are frequent disturbances in the activity of the gastrointestinal tract, including vomiting and diarrhoea. Taken together with the bronchospasm, this points to a response of the smooth muscle to vanadium exposure. Some affected persons have cutaneous manifestations of toxicity in the form of rashes and eczema with itching papules and dry patches (Browne, 1955; Zenz et al., 1962).

Bronchitis and bronchopneumonia are features of severe toxic effects. Other symptoms may also be more prominent, such as headache, vomiting, diarrhoea, palpitations, sweating, and general weakness. Disorders of the nervous system include severe neurotic states and tremor of the fingers and hands (Wyers, 1946; Sjöberg, 1955). Functional disturbances of the

respiratory system can be expected, and X-ray examination will reveal intensification of the lung pattern.

Kidney damage, highlighted by grave dystrophic changes in the epithelium of the convoluted tubules and disturbed tubular secretion, occurs immediately after the start of exposure to low vanadium doses in both acute and chronic intoxication. Once triggered off, the changes are irreversible, even if exposure is discontinued. Therefore, the kidneys are a critical organ for vanadium poisoning (Korkhov, 1965).

8.2.2 Chronic toxicity

Chronic vanadium intoxication produces profound changes in the respiratory organs, because of the irritant action of vanadium and the biochemical and functional disturbances connected with its general resorptive action. Chronic respiratory illness takes the form of diffuse pneumosclerosis, chronic bronchitis, chronic rhinitis, and pharyngitis (Roshchin, 1968). However, Parkes (1982) claimed that the available evidence (Sjöberg, 1950; Williams, 1952; Zenz & Berg, 1967) did not support the contention that prolonged exposure to vanadium compounds leads to chronic bronchitis, with or without emphysema. Although wheezing is more common among vanadium pentoxide workers than among unexposed workers, lung function tests and chest radiography have not revealed persistent lung damage (Kiviluoto, 1980). The cardiovascular system (Wyers, 1946; Sjöberg, 1950; Izycki et al., 1971) is commonly affected in chronic respiratory disorders by a diagnosable accentuated second cardiac sound on the pulmonary artery and an attenuated first sound on the apex cordis. Most of these workers exhibit heavy sinus arrhythmia and a shift of the EGG-axis to the right. After extensive exposure, workers may develop bradycardia and a change of the P wave in the second and third standard leads; coronary spasm is also usually recognizable in such workers. A statistically significant increase in the incidence of enlarged liver and a decrease in functional tests together with bilirubinaemia and a direct reaction to bilirubin have been seen in the blood of exposed workers (Roshchin, 1968). Biochemical alterations have also been found, such as reduction in albumins, and expansion of the globulin fractions at the expense of gamma-globulins, even though the total protein content remained normal. Furthermore, a marked reduction in sulfhydryl groups in blood-serum and in vitamin C levels in the blood, and a less marked drop in cholesterol levels have been observed. Systemic effects, such as a tendency towards anaemia and leukopaenia, and basophilic granulation of leukocytes have been reported (Watanabe et al., 1966).

Vanadium levels in whole blood and serum have been studied to investigate the possible role of vanadium in depressive states. In a study involving neutron activation analysis of vanadium levels in the whole blood, serum, and hair of patients suffering from mania or depression, and of patients who had recovered from these conditions, as well as normal controls, manic patients were reported to have normal levels in whole blood and serum, but significantly raised levels in hair. Depressed patients had raised levels in whole blood and serum. In both conditions, raised levels fell with recovery. The

levels of vanadium in serum were correlated with those in whole blood but not with hair levels (Naylor et al., 1984). In another study, serum-vanadium levels, measured by neutron activation analysis, were reported to be 3.10 ± 1.38 mg/litre in patients suffering from depressive illness and 0.67 ± 0.32 µg/litre in normal subjects (Simonoff et al., 1986). However, in a series of 25 depressive, 13 recovered depressive patients, and 24 controls, the whole-blood concentrations of vanadium were similar to normal levels, and vanadium levels did not change in depressive patients after recovery (Ali et al., 1985).

8.2.3 Diagnosis

Information on likely exposure, the clinical picture, and certain biochemical indications of probable exposure can aid diagnosis, but no specific test can be recommended. Determination of the vanadium contents of the blood and especially of the urine provides documentation of exposure, though the correlation between vanadium levels in the urine or serum and air is poor (Kiviluoto et al., 1979a,c). In view of the work of Schroeder et al. (1963), it would seem desirable to measure the vanadium contents of the serum separately from that of the cellular elements, since the concentration of vanadium in the latter may be more indicative of exposure levels. As reported by Watanabe et al. (1966), a decreased urinary output of ascorbic acid may be one characteristic of vanadium exposure, but differences from controls do not appear sufficient to make the test clinically useful.

Green colouration of the tongue is also an indication of vanadium exposure (Wyers 1946; Williams, 1952; Lewis 1959b). The green hexaquo ion $(V(H_2O))_6^{3+}$ is probably responsible for the green-coloured tongue. However, several other bright green complexes of vanadium^{+4} are known and may also account for the sign (Cotton & Wilkinson, 1962; Durrant & Durrant, 1970). The "green tongue" may be absent, even in prolonged exposure (Sjöberg, 1950).

During continuous exposure, measurement of the cystine content of fingernails was reported to be a sensitive indicator of exposure. This parameter was negatively correlated with vanadium exposure in workers. A decrease in cystine levels in fingernails was demonstrated when urinary-vanadium levels were only 0.02 - 0.03 mg/litre (Mountain et al., 1955). A similar reduction in the cystine content of rat hair was noted when vanadium in the diet ranged from 25 -1000 mg/kg (Mountain et al., 1953). Some evidence suggesting that vanadium may directly inhibit the synthesis of cystine or cysteine has also been reported (Mountain et al., 1953, 1955).

In a recent study on workers exposed to low levels of vanadium pentoxide (0.1 - 0.6 mg/m^3) for about 14 years, Kiviluoto et al. (1980) could not corroborate the observations by Mountain and co-workers as no differences were found in fingernail cystine contents between the 22 exposed workers and 22 unexposed controls. A small reduction in the cystine content of fingernails (89 mg cystine/kg fingernail for exposed and 99 mg/kg for controls) was found by Thürauf et al. (1979) in 54

exposed workers with an increased urine-vanadium concentration of 37.8 µg/litre (controls 0.8 µg/litre).

8.2.4 Treatment of poisoning

There are few published data on the treatment of human poisoning by vanadium. BAL has been used successfully in two cases of overexposure (Sjöberg, 1955). Experimentally, ascorbic acid in doses of 125 mg/kg body weight given 20 min prior to an

LD_{70} dose of $NaVO_3H_2O$ had a strong protective effect in mice (Mitchell & Floyd 1956). $CaNa_2$-EDTA was also antidotal in dogs, when given intraperitoneally in doses of 100 mg/kg body weight after the first sign of poisoning became evident and again 2 and 4 h later. Jones & Basinger (1983) tested various chelating agents and their protective effects in mice and found that efficient antidotes for both vanadate (VO_3^{3-} and vanadyl (VO^{2+}) were ascorbic acid, deferoxamine D-penicillamine, sodium, calcium, $Na_3CaDTPA$, $Na_2CaEDTa$, and glutathione. Ascorbic acid appeared best suited for human use as an antidote.

Intraperitoneal doses of $NaVO_3$ (0.3 - 1.2 mmol/kg body weight) were injected in mice followed by chelating and reducing agents at one-quarter of their respective LD_{50}s. Significant increases in the survival rate, 14 days after the treatment, were noted with ascorbic acid, deferoxamine, and tiron (4,5-dihydroxy-1,3-benzene-disulfonic acid). Other chelators tested included EOTA, DTPA (Na_3Ca-diethylene triaminepenta-acetate) and L-cysteine. Ascorbic acid was the most effective substance in preventing vanadium intoxication (Domingo et al., 1986). In another report, sodium salicylate and D-L-penicillamine were found useless as antidotes for acute toxicity caused by $NaVO_3$.

8.3 General Population Exposure

8.3.1 Low vanadium intake

Because conditions required to achieve reproducible vanadium deficiency in animals have not been defined precisely, it is difficult to predict the consequences of a low vanadium intake on human health.

Statistical studies have shown negative correlations between environmental levels of vanadium and certain other trace elements and the incidence of cardiovascular disease. Consumption of hard water containing vanadium was associated with a lower incidence of cardiovascular disease (Strain, 1961)[a]. Schroeder (1966) reported a significant negative correlation between the vanadium content of municipal waters and death rates due to arteriosclerotic heart disease. In a study by Voors (1971) on the correlation between 7 metals (calcium, chromium, lithium, zinc, manganese, nickel, vanadium) and arteriosclerotic heart disease, a low vanadium intake was associated significantly with a higher incidence of arteriosclerotic heart disease in non-white populations, but no direct correlation was demonstrated for white populations.

[a] Strain, W.H. (1961) *Effects of some minor elements in animals and people.* Paper presented at the meeting of the American Association for the Advancement of Science, Denver, 29 December 1961 (unpublished).

In a joint WHO and IAEA study on the role of trace elements in the etiology of cardiovascular diseases in 20 countries, a significant role was shown for environmental lack of vanadium as well as chromium, zinc, manganese, calcium, and magnesium (Masironi, 1969). Conversely, Hickey et al. (1967) noted a positive correlation between airborne vanadium levels and the incidence of cardiovascular disease (section 8.3.2).

The evidence implicating vanadium as an essential trace element for human beings is not satisfactory. Although certain statistical studies have indicated that low vanadium intake may be associated with human cardiovascular disease, these relationships do not furnish any direct proof for a nutritional role of vanadium in human health. However, they do suggest leads for further laboratory and epidemiological investigations.

8.3.2 Epidemiological studies

Descriptive epidemiological work has been published using a correlational approach, which has well-known limitations, though it imitates a population-based cohort study.
Despite their limitations, such studies can give indications for more intensive and detailed controlled studies into suspected health hazards, comparing incidences of diseases in defined exposure groups (such as production workers) with those obtained from reference populations.

Stocks (1960) reported the results of a study in which airborne concentrations of 13 trace elements were correlated with mortality from lung cancer, pneumonia, and bronchitis in 23 localities in the United Kingdom. At concentrations ranging from 1.1 to 42 $\mu g/1000\ m^3$, vanadium showed a weak association with mortality from lung cancer (taking into consideration population density, sex, and age), with a correlation coefficient of 0.347. Airborne vanadium levels were also correlated with mortality from pneumonia in males, with a correlation coefficient for mortality from pneumonia of 0.443. For mortality involving bronchitis, vanadium gave a correlation coefficient of 0.563. Vanadium also showed an association with mortality from cancers other than lung cancer in males, but not in females. However, in this study, as is usual in studies of this kind, it is not certain that cases of interest (lung cancer, pneumonia) had been exposed at all. There are also the uncertainties of mortality data and failure to consider confounding factors.

In another study, Hickey et al. (1967) considered 10 metals in the air, including vanadium, in 25 communities in the USA. Various techniques, including canonical analysis, were used to correlate airborne metal concentrations with mortality indices

for 1962 and 1963 involving 8 disease categories. The mean atmospheric concentrations for vanadium at the various locations ranged from 0.001 to 0.672 $\mu g/m^3$. The incidence of several diseases, including "diseases of the heart", nephritis, and "arteriosclerotic heart", could be correlated reasonably well with air levels of vanadium and other metals. A high inter-correlation between vanadium and nickel was unexplained. This study was of a very preliminary nature, with no adjustments for the basic pertinent variables normally employed. Other studies have demonstrated significant negative correlations between the incidence of cardiovascular disease and environmental levels of vanadium (section 8.3.1).

An additional multivariate analysis of air-vanadium levels in relation to selected white male mortality levels was included in an unpublished US Environmental Protection Agency staff study by Pinkerton et al. (1972)[a]. Several categories of cardio-vascular disease were used, and also influenza-pneumonia. Vanadium was not correlated with the latter, but was correlated with the cardiovascular categories. However, adjustment for population density produced a considerable reduction in some of these relationships. It was concluded that the observed statistical associations of air-manganese and air-vanadium levels were not causal associations, and represented either a reflection of other more directly associated causes or statistical artifacts.

Barannik et al. (1969) studied the role of certain trace elements and the natural radioactivity of food products in the etiology of endemic goitre in the USSR. More chromium and vanadium and less lead were found in most of the vegetable products from a region where goitre was endemic compared with those from a goitre-free region. The differences in the mean concentrations of these trace elements were statistically significant.

The differences between these general population-based observations and the occupational studies on health effects in vanadium workers (section 8.3) are connected to different approaches. The correlational epidemiological studies, based exclusively on long-term effects and causes of death, are considered at the expense of lack of individual exposure data, while the medical studies, cross-sectional in nature, cannot consider the selection effects and lack long-term information (such as cause of death). Their strength, however, lies in the fact that they permit analysis according to different levels of exposure, though further occupational and population studies on chronic illness in unambiguous relationship to vanadium exposure are needed to verify previous work and determine if there is evidence of a dose-response relationship. In such studies, morbidity as well as mortality should be considered.

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[a] Pinkerton, C., Hammer, D.I., McClain, K., Williams, M.E., Bridbord, K., & Riggins, W.B. (1972) *Relationship of* manganese and vanadium in the ambient air to heart disease and influenza-pneumonia mortality rates, Research Triangle Park, North Carolina, US Environmental Protection Agency

(unpublished data).

8.4 Occupational Exposure

Occupational poisoning occurs mainly during the industrial production and use of vanadium and in boiler cleaning operations. Under these conditions, vanadium may enter the human body through the respiratory tract; an unknown quantity will be transported to the alimentary tract when swallowed. Vanadium can also enter through the skin (Roshchin, 1968).

Both acute and chronic poisoning can occur. Vanadium-containing industrial aerosols differ in chemical and structural composition and thus evoke different responses in the human body.

In sections 8.3.1 - 8.3.4, a survey is made of the available clinical and epidemiological data on the health effects of vanadium in workers occupationally exposed to vanadium compounds. Most of the reported clinical symptoms reflect irritant effects of vanadium on the respiratory tract and eyes.

8.4.1 Metallurgy

Dutton (1911) first described the effects of industrial exposure to vanadium-bearing ores. He reported a dry, paroxysmal cough with haemoptysis and irritation of the eyes, nose, and throat. Temporary increases in haemoglobin levels and red blood cells were followed by reductions in both and the onset of anaemia. Vanadium was recovered in all bodily secretions. Postmortem examination revealed highly congested lungs with destruction of the alveolar epithelium and congested kidneys with evidence of haemorrhagic nephritis. Unfortunately, the workers frequently suffered from pulmonary tuberculosis, which undoubtedly produced many symptoms that were aggravated by vanadium exposure, and no details regarding the number of workers examined or the incidence of the signs and symptoms were provided.

A later study by Symanski (1939) on relatively healthy metal workers exposed to vanadium pentoxide dust for periods ranging from a few months up to several years reported severe conjunctivitis, rhinitis, pharyngitis, chronic productive cough, and tightness of the chest; severe chronic bronchitis and bronchiectasis sometimes occurred with longer exposure. There was no evidence of a generalized systemic action of vanadium.

Rundberg (1939) observed bronchitis with purulent sputum, general weakness, and skin irritation of the face and hands in 20 men handling vanadium pentoxide in a metallurgical works. Productive cough, bronchitis, and shortness of breath were reported by Balestra & Molfino (1942) in 25 workers exposed to vanadium pentoxide dust from petroleum ash. Other substances were involved, and chest X-rays showed definite lung markings suggesting pneumonoconiosis. Bronchiectasis was suspected in 2 cases.

Studies were reported by Wyers (1946, 1948) on 50 - 90 workers exposed to vanadium pentoxide as an oil combustion residue and to slag from the production of ferrovanadium.

Findings included bronchospasm, often with elevated blood pressure and accentuated pulmonary second sound, a paroxsymal cough, dyspnoea, skin pallor, tremor of fingers, palpitation, chest pains, and reticulation of the lungs. Wyers emphasized the irritant effects of vanadium pentoxide on the respiratory tract, but also found evidence of systemic toxicity.

An extensive report including data on the dust contents of the air in a metallurgical plant producing vanadium pentoxide was published by Sjöberg (1950). The dust particles were relatively large in size (39% less than 12 μm, 22% less than 8 μm). It was estimated that a concentration of 6.5 μg V_2O_5/m^3 represented the worst exposure conditions. Thirty-six men between 20 and 50 years of age had been employed in the plant since 1946: 22 had a dry cough; wheezing sounds could be detected in 31; and 27 were short of breath. One man developed acute pneumonitis, and 4 others developed bronchopneumonia. There was no evidence of systemic toxicity.

A dry eczematous dermatitis developed in 9 men in Sjöberg's (1950) study, but only 1 man showed a positive patch test. Sjöberg (1951) and Sjöberg & Rigner (1956) believed that allergy might play a role in the development of eczema and pneumonitis following vanadium exposure. Zenz et al. (1962) also considered this an explanation for the more severe symptoms found on re-exposure in their study. In a follow-up to the 1950 study, Sjöberg & Rigner (1956) reported that the 16 men most severely affected still complained of shortness of breath, cough, fatigue, and wheezing. Bronchitis was present in 2 men. However, spirometric measurements, cardiac function tests, electrocardiograms, haematological tests, and urinanalyses were essentially normal.

Lewis (1959b) studied 24 male workers in an environment in which the maximum exposure was only 0.925 mg vanadium (as $V_2O_5)/m^3$ of air. In most cases, the exposure was to 0.3 mg vanadium/m^3. More than 92% of the dust particles were smaller than 0.5 μg in every process area sampled. Symptoms of cough with sputum production, eye, nose, and throat irritation, and wheezing were related to physical findings of wheezes, rales, or rhonchi, injected pharynx, and green tongue. All of these symptoms and physical findings were statistically significant in comparison to those in 45 referents (Tables 25 and 26).

A report by Rajner (1960) on 30 vanadium workers in a metallurgical plant described particularly severe signs and symptoms, but did not give any estimates of exposure except in conjunction with urinary-vanadium levels. In acutely poisoned workers, vanadium values were about 4000 μg/litre urine. The average value among permanent employees was 45 μg/litre; vanadium pentoxide smelter workers had maximum values of about 400 μg/litre. When a new production process was introduced, symptoms of acute vanadium poisoning occurred in 3 workers after

16 h of work including severe respiratory difficulties, headache, dejection, and loss of appetite. Acute inflammatory changes of the upper respiratory tract with copious mucous production, oedema of the vocal cords, and profuse epistaxes were reported. All workers who had been exposed for a long time

(up to 22 years in 27 subjects, mostly in ferrovanadium and vanadium pentoxide smelting operations) complained of coughing and eye, nose, and throat irritation, breathing difficulties during physical exertion ("more than two-thirds of the workers"), and headache (12 cases). Clinical findings included intense hyperaemia of the mucosa of the nasal septum in 20 workers; perforation of the nasal septum was seen in 4 workers exposed for an average of 18 years. Intense hyperaemia of the mucosa of the throat and larynx with dilated fine capillaries was found in 50% of the workers. Bronchoscopy indicated the presence of chronic bronchitis, and bronchial smears revealed sloughed epithelium.

Matantseva (1960) studied 77 workers in contact with vanadium pentoxide in the form of dust and fume in concentrations exceeding the MAC value (dust = 0.5 mg/m^3; fumes = 0.1 mg/m^3) for periods ranging from 1 to 12 years. Nearly all the subjects had various complaints relating to the upper respiratory tract including unpleasant sensations in the nose, a liquid mucous discharge from the nose, obstructed nasal breathing, a sensation of burning and dryness in the nasopharynx, scratching, dryness, and tickling in the throat, hoarseness of the voice, and cough. Physical examination showed rhinitis, which was of a simple catarrhal form in workers exposed for less than 3 years, a hypertrophic and subatrophic form if the exposure was for more than 3 years, and an atrophic form if the exposure was for between 7 and 12 years. Examination of the lungs revealed acute and chronic lesions in the form of bronchitis, peribronchitis, and pneumosclerosis. Hyperventilation and an elevated basal metabolic rate were noted.

Table 25. Symptoms in 24 vanadium workers and 45 unexposed referents[a]

Symptom	Incidence (%)		X^2 value
	Referents	Exposed	
Cough	33.3	83.4	13.71[b]
Sputum	13.3	41.5	5.55[c]
Exertional dyspnoea	24.4	12.5	0.592
Eyes, nose, throat irritation	6.6	62.5	23.17[b]
Headache	20	12.5	0.124
Palpitations	11.1	20.8	0.538
Epistaxis	0	4.2	0.148
Wheezing	0	16.6	5.20[c]

[a] From: Lewis (1959b).
[b] Significant beyond P = 0.01.
[c] Significant at $P = 0.02$.

Table 26. Physical findings in 24 vanadium workers and 45 unexposed referents[a]

Physical finding	Incidence (%)		X^2 value
	Referents	Exposed	
Tremors of hands	4.5	4.2	0.0320
Hypertension	13.3	16.6	0.0002
Wheezes, rales, or rhonchi	0	20.8	6.93[b]
Hepatomegaly	8.9	12.5	0.003
Eye irritation	2.2	16.6	2.94
Injected pharynx	4.4	41.5	12.62[b]
Green tongue	0	37.5	14.53[b]

[a] From: Lewis (1959b).
[b] Significant beyond $P = 0.01$.

Roshchin (1963b) published an account of the effects of vanadium-containing Bessemer slag dust on 45 workers. Dust concentrations in the air during various phases of this operation ranged from 5 to 150 mg/m^3, with the highest concentrations occurring during loading/unloading of broken slag as the trivalent oxide, mostly within spinellide. Repeated examinations of the 45 workers showed the slag dust to have an effect on the respiratory mucosa. Subatrophic rhinitis, bronchitis, and pneumosclerosis were seen in subjects with long occupational exposure (11 workers). Chronic bronchitis was found in every worker employed for 5 years or more. Clinical and X-ray examination of all 45 subjects showed radiological changes in 24 employed for 10 years or more; in 11 subjects, pneumoconiosis of stage I-II was diagnosed. X-ray examination showed diffuse sclerotic changes over the whole extent of the lung fields (except for the supraclavicular zones), small focal opacities, intensified and enlarged shadows at the root of the lungs, and marked signs of bullous emphysema. Predominant involvement of the lower regions of the lungs (characteristic of silicosis) was not present. This pneumosclerosis was accompanied by changes in the cardiovascular and nervous systems, biochemical disturbances (hyper-vitaminosis with dysproteinaemia and an increase in the serum concentration of sulfhydryl groups), a tendency to anaemia and leukopaenia, and changes in the liver.

In another study, Roshchin (1964) described chronic effects of vanadium in 193 workers who had been exposed to aerosols of free vanadium pentoxide: 127 worked in vanadium metallurgy and 66 were boiler cleaners (section 8.3.2). The length of occupational contact with vanadium was over 10 years for 60%, from 5 to 10 years for 30%, and under 5 years for the remaining 10%. Practically all complained of irritation of the nasal and pharyngeal mucosa including itching, a profusely running nose (especially during work), and unpleasant sensations in the

throat and nose. Epistaxis was frequent in 20%. Physical examination revealed a high incidence of changes in the nasal mucosa: dryness (40%), erosion (23%), scars (8%), perforation (4%), hyperaemia (10%), and hypertrophy (7%). Also noted were dryness of the pharynx (5%), hyperaemia of the pharynx (5%), hyperaemia of the larynx (4%), and tonsillitis (5%). The most common pathological changes in the upper respiratory tract were subatrophic rhinitis (40%) and destructive changes in nasal mucosa (35%), while hypertrophic rhinitis was less frequently seen (7%). The overwhelming majority had a dry cough; cough with viscid sputum was less common. Workers with longer occupational exposure complained of shortness of breath, which appeared sometimes after 5 but mostly after 10 years of work in the industry. Nearly all complained of aching or shooting pains in the chest and of lassitude and weakness. The main respiratory diseases diagnosed were chronic bronchitis (40%) and diffuse pneumosclerosis (13%). Haematological tests showed the total serum-protein concentration to be normal, y-globulins to be raised (19.4% compared with 12.2% in controls), and the albumin-globulin ratio to be 1:1 - 1:2 (1:9 in controls). Determination of total, residual, and protein sulfhydryl groups in the blood-serum revealed a marked decrease of 7 - 13% compared with the controls. Regular observations over a period of 14 years showed that the chronic bronchitis tended to get worse, with development of bronchospasm. After a long period of time, some subjects developed pneumosclerosis; in others, the disease progressed slowly from chronic bronchitis to diffuse pneumosclerosis and pulmonary emphysema.

Eisler et al. (1968) studied 48 metallurgical workers occupationally exposed to vanadium for between 17.6 ± 9 years. Definite clinical evidence of chronic bronchitis was present in 90% of the subjects, and 50% had severe obstructive bronchitis. In control groups, which included basic-slag crushers and furnace operators (99 and 50, respectively), chronic bronchitis was observed in 33% and 26%, respectively.

A study on 13 workers engaged in the extraction and refining of vanadium pentoxide from soot generated by the combustion of heavy fuel oil was reported by Nishiyama et al. (1977). Concentrations of vanadium in the air at various locations in the work environment were all less than 0.5 mg/m^3 (mean, 1.2 - 12 μg/m^3). There was a significant incidence of injection of the pharynx (58.3%) compared with controls. Elevated levels of vanadium in the urine and hair were detected both in currently-exposed as well as in previously-exposed subjects. Apart from a slight depression in serum-cholesterol levels, haematological results were normal.

Roshchin (1968) analysed the incidence of influenza and upper respiratory catarrh as a cause of lost working time in workers in vanadium metallurgical plants compared with ferrous metallurgical workers in adjacent plants. The results are given in Table 27. The morbidity was consistently higher among workers producing vanadium than among workers in other departments in all years.

Table 27. Morbidity from influenza and upper respiratory catarrh[a]

Department	Cases (per 100 workers)				Days off work (per 100 workers)			
	1958	1959	1960	1962	1958	1959	1960	1962
Vanadium plant	40.6	68.4	58.8	59.8	180.6	376.7	271.9	336.5
Open hearth furnace	22.2	53.2	45.6	62.1	76.9	331.1	176	213.3
Blast furnace	21.9	46.7	37.8	47.6	36.3	262.8	166.6	215.5
Engineering shop	19.6	39.1	33.9	44.9	86.8	224.8	154.3	223.6

[a] From: Roshchin (1968).

Asthma was reported in 4 workers exposed to vanadium pentoxide dust in a newly established vanadium pentoxide refinery (Musk & Tees, 1982). One of the workers had positive skin tests to environmental allergens; the others were non-atopic. Three were smokers; one was an ex-smoker. One of the subjects experienced irritation of the upper respiratory tract after a single exposure; dyspnoea and wheezing developed 2 weeks later. All workers had similar irritant symptoms and green tongue. Two showed bronchial hyperreactivity when challenged with histamine; these were the workers with the most recent exposure. In one worker, the asthmatic symptoms continued for 8 weeks after cessation of exposure. There was no indication of an immunological aetiology, and the authors concluded that the effect was likely to be a direct chemical one.

Kiviluoto et al. (1979a,b, 1980, 1981a,b) and Kiviluoto (1980) reported the results of a cross-sectional study on 63 males exposed to vanadium-containing dust in a vanadium factory; a reference group matched for age and smoking was selected from a magnetite ore mine. The workers had been exposed to vanadium dust for an average of 11 years at concentrations ranging from 0.1 to 3.9 mg/m^3 (estimated average exposure levels of 0.2 - 0.5 mg/m^3); the respirable fraction ($\leq$ 5 μm) was 20%. Nasal biopsies and lung function tests were taken at the end of the summer holidays (duration, 2 - 4 weeks). Nasal smears and biopsies were repeated in 31 workers, 7 - 11 months later, after hygienic improvements had reduced the exposure levels to 0.01 - 0.04 mg/m^3. Microscopic examination of nasal smears revealed a significant increase in neutrophils and biopsies of nasal mucosa showed significantly elevated numbers of plasma and round cells in the exposed workers. There was no further increase in the cell findings after 10 months of exposure to 0.01 - 0.04 mg/m^3 vanadium dust; eosinophils did not show any differences between the exposed and the referents. The authors attributed these findings to "an irritating effect of vanadium dust on the mucous membranes of the upper respiratory tract". Biopsies from workers with the longest exposures (170 - 241 months) showed "a zone-like sub-epithelial infiltration of mononuclear cells and frequent papillarity in the mucous membrane surface with its hyperaemic capillaries". The similarity between this pattern and that seen in vanadium-exposed rabbits (Sjöberg, 1950) was noted (Kiviluoto et al., 1979b). A random sample of 12 nasal biopsies was further investigated for the amount and classes of

immunoglobulins (IgE, IgG, IgM, and IgD). IgG subclasses were not studied. There were no differences between the 12 workers and their referents, which was construed as a further indication of non-specific inflammation (Kiviluoto et al., 1981b).

Pulmonary condition was assessed by means of questionnaires, X-ray, and pulmonary function testing. There was only one significant difference between the workers exposed for an average of 11 years to 0.1 - 3.9 mg/m^3 (estimated average, 0.2 - 0.5 mg/m^3) and at the time of investigation to 0.01 - 0.04 mg/m^3, and their matched referents; complaints of wheeze were more common in the exposed worker group (Kiviluoto, 1980). The importance of this finding remained doubtful. It may reflect the respiratory findings mentioned above, since upper respiratory irritation may be accompanied by transient reflex bronchospasm. A series of laboratory tests were designed to evaluate electrolyte, protein fractions, carbohydrate, and lipids, liver, renal, muscle, pancreatic, and bone marrow functions, and immunological status. There were no decreases in serum-cholesterol or triglycerides, and no clinical differences between worker and control groups (Kiviluoto et al., 1981a).

The effects of vanadium compounds on health is not confined to the development of local respiratory or other lesions. Various studies, most of them rather old, on patterns of lost working time due to morbidity have shown that the incidence of disease among workers in plants producing vanadium compounds is considerably higher than among other workers (Symanski, 1939; Syers, 1946; Sjöberg, 1950, 1956; Reznik, 1954; Reinl, 1958; Matantseva, 1961; Watanabe et al., 1966; Roshchin, 1968, 1969; Athanassiadis, 1969; Schumann-Vogt, 1969; Chiriatti, 1971). The most significant differences are found in the incidences of influenza, upper respiratory catarrh, and inflammation of the lungs. The difference in the incidence of bronchitis is particularly marked.

8.4.2 Cleaning and related operations on oil-fired boilers

Bronchitis and conjunctivitis resulting from exposure to soot (containing 6 - 11% vanadium) during the cleaning of the stacks of oil-fired boilers were first recognized by Frost (1951). Frost did not report any other effects, but, in a subsequent report of a boiler-cleaning operation by Williams (1952), sneezing, nasal discharge, lachrymation, sore throat, and substernal pain occurred within 0.5 - 12 h of exposure. Within 6 - 24 h, secondary symptoms developed; these consisted of dry cough, wheezing, laboured breathing, lassitude, and depression. In some cases, the cough became paroxysmal and productive. Symptoms lessened only after removal from the working environment for 3 days. Air sampling showed most of the dust particles to be smaller than 1 µg. The vanadium concentration ranged from 17.2 mg/m^3 in a superheater chamber to 58.6 mg/m^3 in a combustion chamber. Roshchin (1962) observed 8 cases of acute vanadium poisoning in workers who cleaned boiler flues at power stations burning high-sulfur oil. Analysis of soot deposits showed that the soot in the region of greatest dust formation (the pipes of the steam superheater and water economizer) contained from 24 to 40% vanadium pentoxide. The workers carried out cleaning operations without respirators or with respirators that did not provide the necessary protection.

After cleaning the boilers, the workers developed acute vanadium poisoning: itching in the throat, sneezing, cough with difficult expectoration, and smarting eyes. On the following days, the symptoms became more severe. Tightness in the chest, sweating, general weakness, conjunctivitis, and noticeable loss of weight developed. On examination one week later, hyperaemia and oedema of the fauces and posterior pharyngeal wall were observed. Harsh breathing sounds and dry crepitations were heard in the lungs. X-ray examination showed intensified lung markings in the middle zones of the right and left lungs and thickening of the fissure on the right. One month later, only one worker still had cough, weakness, perspiration, loss of energy, and dyspnoea. The other workers recovered quickly, with complete disappearance of cough and shortness of breath.

In another study on workers engaged in boiler-cleaning operations (Troppens, 1969), the symptoms were described as similar to mild coryza or influenza with bronchitis. Following recovery, workers were tired, debilitated, irritable, without any appetite, and complained of watery eyes. The first symptoms were swelling of face and eyes as early as 20 min after entering the boiler area. Removal from exposure for 2 - 3 weeks resulted in the disappearance of symptoms. Skin blemishes described as allergic dermatoses were attributed to absorption of vanadium through sensitive skin. Troppens claimed that there was an increased susceptibility of the vanadium worker to asthmatic bronchitis and emphysema.

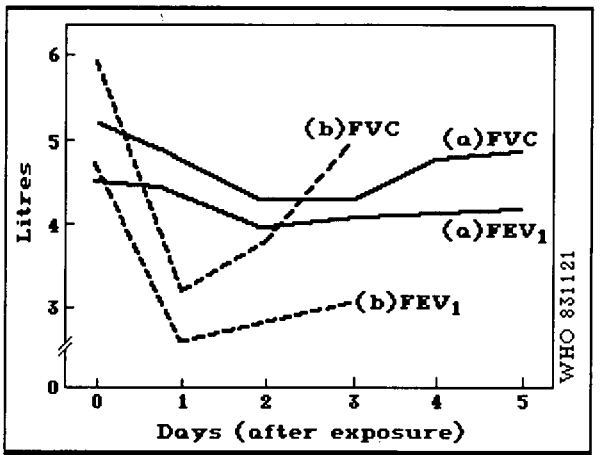
An investigation is reported on 53 workers performing emergency repair work on oil-fired power station boilers (Izycki et al., 1971). They were exposed to vanadium pentoxide in average concentrations of from 1.2 to 11 mg/m^3 and also to manganese, calcium, and nickel oxides, and sulfur compounds. Characteristic features of both acute and chronic vanadium poisoning included upper respiratory catarrh in 45%, increased lung markings in 24.5%, and bradycardia in 22% of cases. Persistent chronic changes in the respiratory tract (rhinitis, pharyngeal catarrh, laryngitis, and changes in the paranasal sinuses) were present in 45%.

Milby (1974) reported 21 cases of vanadium poisoning in boilermakers installing new catalytic-converter tubes. This work involved marble-sized pellets of vanadium containing 11.7% V_2O_5. The dust formed during the shaking of these pellets had a particle size of 1.1 - 1.5 μm. After working for 72 h, the workers began to complain of nasal, eye, and bronchial irritation. By the 4th day, most felt very ill, with signs of irritation of the upper respiratory tract and eyes and pains in the chest.

In a study by Garlej (1974) 50 workers engaged in the cleaning of oil-fired boilers were compared with a control group of 60 other workers. Boiler deposits contained 44 -65% V_2O_5; the maximum exposure was estimated to be 10 mg/m^3. Although no clinical evidence of vanadium poisoning was seen, a number of exposure-dependent positive biochemical reactions were found in the boiler-cleaning group. Urinary excretion of delta-amino-levulinic acid (ALA), porphobilinogen (PBG), and porphyrin

increased beyond the physiological limit, and the positive Nadi reaction (with associated green fluorescence) occurred. The increased excretion of cytochrome (as indicated by the Nadi reaction) suggested oxidation through V_2O_5 of the thiol group -SH cysteine in the protein carrier, resulting in decreased binding of cytochrome in the mitochondria.

A study on 17 men who were engaged in cleaning boilers at an electric generating station was reported by Lees (1980). In addition to clinical findings, which were similar to those described above, urine-vanadium levels were determined, and pulmonary function measurements were made for a week following exposure. Sixteen of the men wore protective clothing, and respirators that were found to have about 9% leakage. One workman volunteered to wear only a simple oro-nasal dust mask for 1 h of exposure. The dust exposure level was estimated to be 26 mg/m^3; respirable dust (under 10 μm) was measured at 523 μg/m^3 with a vanadium content of 15.3%. All of the men developed reduced pulmonary function that had not fully returned to normal in one week, but did so after one month. Reduced function outlasted the clinical symptoms by several days. Fig. 3 shows the contrast in pulmonary reaction between the more heavily exposed individual and one of the other workmen. The urine-vanadium level of the volunteer was 280 μg/litre, whereas those of the remainder of the workers were below 40 μg/litre.



Reduction in lung function following (a) light and (b) heavy exposure to vanadium compounds.

Other observations of boiler-cleaning operations have been made by Fallentin & Frost (1954), Sjöberg (1955), Thomas & Stiebris (1956), Hickling (1958), and Kuzelova et al. (1975). In terms of respiratory symptoms relating to boiler-cleaning, it should be noted that sulfates and sulfuric acid may be present in boiler soot and may be partly responsible for irritative effects. Hudson (1964) suggested that the quick onset of symptoms (lachrymation with nose and throat irritation) with rapid recovery following removal from exposure is characteristic of exposure to acid sulfates. Response to vanadium exposure is characterized by some delay in the onset of irritative symptoms (a few hours to several days) and persistence of symptoms following removal from exposure (Hudson, 1964).

A recent report by Levy et al. (1984) concerned a comparatively high incidence of severe respiratory tract irritation in boilermakers (74/100), many of them welders in areas without adequate ventilation, exposed to vanadium pentoxide fumes in a power plant where conversion from oil- to coal-burning occurred. The severe illness of 70 men caused an average of 5 days of absence, some objective tests (e.g., FVC) being markedly affected. The vanadium pentoxide content was above the permissible exposure limit in 8 samples, and this resulted in litigation for inadequate protection of the workers.

Kuzelova et al. (1977) drew attention to the occupational risk of chimney sweeps cleaning large-capacity heating facilities in large housing settlements. This coincided with a report of a detailed cross-sectional examination of 121 chimney sweeps by Holzhauer & Schaller (1977) in the Federal Republic of Germany with an average exposure duration of 19 years (± 5 years). Vanadium exposure was determined by personal samples, and measurements between 0.73 and 13.7 mg vanadium pentoxide/day were determined compared with 4 μg in the normal (average) population. Urinary excretion was determined to be between 0.15 and 13 μg/litre, which was significantly higher than the values in 31 referents. The main complaints of the chimney sweeps were wheezing, rhinitis, conjunctival irritation, cough, sputum dyspnoea, and hoarseness; there were no skin symptoms. A prospective follow-up of the cohort was emphasized, but the results are not yet available.

8.4.3 Handling of pure vanadium pentoxide or vanadate dusts

Health effects due to occupational handling of pure vanadium pentoxide or vanadate dusts have been reported. Tara et al. (1953) described the effects of vanadium exposure in 4 dock workers who unloaded and bagged spilled calcium vanadate. The symptoms (bronchitic wheezing sounds, dyspnoea, productive cough, haemoptysis in one case, and headache) necessitated interruption of the work after 1′ days. Zenz et al. (1962) described an acute illness that occurred in 18 workers pelletizing pure vanadium pentoxide; it was characterized by a rapidly developing mild conjunctivitis, severe pharyngeal irritation, a non-productive persistent cough, diffuse rales, and bronchospasm. With severe exposure, 4 men complained of itching skin and a sensation of heat in the face and forearms. The symptoms became more severe after each exposure, suggesting a sensitivity reaction, but their duration was not prolonged by repeated exposures.

8.4.4 Other industries

Browne (1955) studied vanadium poisoning in 12 patients exposed to exhaust fumes from gas turbines using heavy fuel oil. Evidence of poisoning appeared between the first and 14th day of exposure and consisted of conjunctivitis, rhinitis, cough, crepitations, and dyspnoea. Bleeding appeared before the rhinorrhoea.

Other occupations in which respiratory effects of vanadium exposure have been reported include operations connected with the gasification of fuel oil (Fear & Tyrer, 1958) and the

manufacture of phosphor for television picture tubes (Tebrock & Machle, 1968). In the latter study, elevated blood pressure was noted in men exposed to vanadium pentoxide.

9. EVALUATION OF HEALTH RISKS FOR MAN

9.1 Environmental Levels and Exposures

While vanadium concentrations in the air of remote rural areas are less than 1 ng/m^3, other rural areas show concentrations in excess of 50 ng/m^3. This is generally considered to reflect the local burning of fuel oil with a high vanadium content. Typical concentrations in urban air may range from below 1 ng/m^3 to over 300 ng/m^3, with annual averages for large cities of about 20 - 100 ng/m^3. At an annual average of 50 ng/m^3 and a respiration rate of 20 m^3, the total amount of vanadium reaching the respiratory tract would be only 1 µg. Assuming a rate of absorption of about 25%, the direct daily contribution of vanadium from air would be about 250 ng.

Drinking-water supplies without excessive vanadium pollution contain from less than 1 µg/litre to occasional maximum concentrations of 15 - 30 µg/litre. Two comprehensive surveys have shown average concentrations of 4.3 and 4.85 µg/litre, respectively. At a daily intake of 2 litres of water, the average daily intake of vanadium with water would be about 10 µg, ranging from about 1 µg to 30 - 60 µg. Although levels in ordinary water supplies would vary considerably, intake should rarely exceed 100 µg/day. Intake with bottled waters from mineral springs may exceed these values.

As a rule, the concentration of vanadium in food is low. High levels reported in early studies have been attributed to analytical differences. Recent studies on complete diets suggest a daily intake of vanadium of about 10 - 70 µg, with the majority of estimates remaining below 30 µg. Assuming an absorption rate from the gastrointestinal tract of 1 - 2%, the contribution from food and water is unlikely to exceed 4 - 5 µg/day.

Vanadium concentrations in air in the vicinity of metallurgical industries are often about 1 µg/m^3. In the production of vanadium metal or compounds, concentrations may reach a few mg/m^3. In boiler-cleaning operations, dust concentrations in air are frequently around 50 - 100 mg/m^3, and concentrations as high as 500 mg/m^3 have been reported; the vanadium content of the dust is about 5 - 17% as vanadium pentoxide and 3 - 10 % as lower vanadium oxides. The need for personal protection devices in such operations is obvious.

9.2 Physiological Role

While present knowledge indicates that vanadium is an essential element for chicks and rats, conclusive evidence that vanadium is essential for other species, including man, is lacking. A variety of physiological and biochemical processes have been found to be vanadium sensitive. However, so far, there is no evidence of adverse effects arising from vanadium deficiency in man, and the daily requirement of vanadium in the

diet is not known.

9.3 Effects and Dose-Response Relationships

The toxicity of vanadium varies in experimental animals with both the species and route of administration. Small animals, such as the rat and mouse, tolerate the metal better than the rabbit and horse. The toxicity of vanadium is low when given orally, moderate when inhaled, and high when injected. As a rule, the toxicity of vanadium increases as the valency increases, pentavalent vanadium being the most toxic.

9.3.1 Local effects and dose-response relationships

Exposure of 2 volunteers to vanadium pentoxide dust at 1 mg/m^3 for 8 h resulted in irritation of the respiratory tract with cough starting 5 h later. The cough lasted for 8 days. Exposure of 5 volunteers to a concentration of 0.2 mg/m^3 caused the same symptoms, i.e., coughing, but with an onset at 20 h. The cough lasted for 7 - 10 days. Respiratory irritation was noted in 2 subjects exposed to 0.1 mg/m^3 for 8 h. The irritant effect was manifested as an increase in mucous production, 24 h after exposure, and total recovery within 4 days. Tickling and itching, together with dryness of the mucous membranes of the mouth, was reported by 11 volunteers exposed to 0.4 mg/m^3 of vanadium pentoxide condensation aerosol; 0.16 mg/m^3 caused irritation in only 5 subjects, and 0.08 mg/m^3 did not induce symptoms in any of the subjects.

Exposure to high concentrations of vanadium is possible in the industrial production and use of vanadium, especially in the cleaning of oil-fired boilers. Frequently reported irritant symptoms include sneezing, nasal discharge, irritation of the eyes with lachrymation, sore throat, dry or productive cough, and chest pain. Normally, such symptoms disappear in a few days when exposure has ceased. Cough, increased sputum, and particularly irritation of the eyes, nose, and throat occurred among 24 male workers exposed to a maximum of 0.9 - 5 mg vanadium/m^3 (measured as vanadium pentoxide V_2O_5). Most workers had been exposed to 0.3 mg/m^3 (section 8.4.1). A cross-sectional study of 63 male workers exposed for an average of 11 years to vanadium-containing dust at 0.2 - 0.5 mg vanadium/m^3 (range, 0.1 - 3.9 mg/m^3) showed chronic irritant effects in the mucous membranes of the nose. The nasal changes persisted unchanged during subsequent exposure to much lower levels (0.01 - 0.04 mg/m^3).

Heavily exposed workers (dust concentrations of 5 - 150 mg/m^3) developed atrophic rhinitis and chronic bronchitis. Bronchospasm is also a feature in heavily exposed workers.

The effects on 63 workers of long-term exposure to vanadium at 0.2 - 0.5 mg/m^3 were studied using matched referents, a questionnaire on respiratory symptoms, chest radiography, and lung function testing (section 8.4). There was no change in ventilatory function compared with the matched reference group; only complaints of wheezing were significantly more common among exposed workers than among referents. However, in another study

the forced vital capacity (FVC) was reversibly reduced in 17 boiler cleaners who had been exposed to a time-weighted average respirable dust of 523 $\mu g/^3$ containing 15% of vanadium (section 8.3.1).

Vanadium poses weak sensitizing properties when skin and mucous membranes of the upper respiratory tract are exposed to high concentrations, manifested by the development of allergic dermatitis and rhinitis in workers in contact with vanadium. The allergic nature of these manifestations is proved by positive reactions of epicutaneous tests with a 2% solution of sodium vanadate. There is information on the sensitizing effect of vanadium in tests on animals.

In one study (section 8.4.1), 9 workers out of 36 developed a dry eczematous dermatitis. These workers had been exposed to vanadium pentoxide at about 6.5 $\mu g/m^3$.

Green tongue is seen in a proportion of workers exposed to vanadium-containing dust, and is an indication of exposure.

9.3.2 Systemic effects and dose-response relationships

9.3.2.1 Metabolic effects

The effect of vanadium on dental caries remains a debatable issue (section 5.4.2). The application of a 50% paste of an ammonium salt of vanadium and glycerol was reported to reduce caries in children aged 7 - 11 years. Other studies between 1955 and 1968 have failed to demonstrate a clearly beneficial effect (section 8.1.2.1).

Soluble diammonium oxytartarovanadate (150 - 200 mg/day for 6 weeks) was administered to 5 healthy adult male volunteers. There was a significant reduction of plasma-cholesterol levels at the end of the period. A temporary drop in the cholesterol level was also observed in 2 out of 6 patients given ammonium vanadyl tartrate for 7 weeks at 50 or 100 mg/day. The results were not convincing and the temporary drops in cholesterol levels were not statistically significant. No significant changes in serum-cholesterol levels were noted in 12 patients (9 of whom were hypercholesterolaemic) given diammonium vanado-tartrate orally for 6 months, (25 mg three times daily for 2 weeks, increased to 125 mg daily in 10 patients). Although some studies on rats and rabbits have indicated decreasing cholesterol levels following administration of vanadium and have corroborated the reduced levels of cholesterol observed by other authors, this effect of vanadium has not been convincingly demonstrated in human beings so far (section 8.1.2.1).

Vanadium pentoxide in the diet (25 - 1000 mg vanadium/kg) resulted in lower levels of cystine in the hair of rats compared with those in controls, indicating the inhibition of cystine synthesis (section 7.2.1). Rats administered sodium vanadate intraperitoneally (5 - 10 mg/kg body weight as a single injection or a dietary concentration of 500 mg/kg) showed reduction of co-enzyme A in the liver; this has been construed as an explanation of the reduction of cystine (section 7.2.1). When workers were exposed to vanadium-containing dust (0.2 -

0.5 mg vanadium/m^3, at the time of the study), there was no correlation between exposure level and cystine levels in fingernails, and no decrease in levels of serum-cholesterol or triglycerides (section 8.4.1).

The data on the effects of vanadium on haematopoiesis are inconsistent. A favourable effect of vanadium chloride (0.6 mg vanadium/kg diet) on haemoglobin levels in rats, previously made anaemic, had already been suggested in 1931 (section 7.2). A small increase in erythrocytes and haemoglobin levels was observed in rabbits given vanadyl sulfate subcutaneously, at 1 mg/kg body weight daily, for 2 months). When 32 vanadium workers who had been exposed for more than 6 months were compared with 45 referents, matched for age, no differences were seen in haematocrit levels (8.2.1.1). It is not possible to assess the effects of low-level vanadium exposure on iron metabolism.

9.3.2.2 Effects on the nervous system

Systemic effects are rare in workers exposed to vanadium compounds. Non-specific signs and symptoms including headache, weakness, nausea, vomiting, and tinnitus have been reported. Such signs and symptoms have mostly occurred in workers exposed to extremely high dust concentrations, when cleaning oil-fired boilers, but it has not been possible to derive dose-response relationships for them.

Elevated vanadium levels in whole blood and serum have been reported in patients suffering from depressive illness. In one report, the vanadium levels fell to normal with recovery of the patients. The role of vanadium in depressive states is not known (section 8.2.2).

In mice and rats, repeated oral administration of vanadium pentoxide or ammonium vanadate at doses of 0.05 - 0.5 mg vanadium/kg body weight, daily, for 6 months and 21 days, respectively, resulted in impaired conditioned reflexes. Daily oral doses of sodium metavanadate (3.2 µg/kg body weight per day for 10 - 15 days) caused increases in the activity of cytochrome oxidase in the brain of guinea-pigs; a dose of 128 µg/kg per day did not have any effect, whereas 5.12 mg/kg per day reduced the activity (section 7.2). Total cholinesterase activity in the brain of rats was significantly reduced by the intraperitoneal administration of 1 mg vanadyl sulfate/kg body weight (section 7.3).

9.3.2.3 Effects on the liver

There are insufficient human data to make an assessment of the effects of vanadium on the liver. Rats and rabbits exposed

through inhalation to vanadium pentoxide, trioxide, or trichloride (10 - 70 mg/kg, 2 h/day, for 9 - 12 months) showed fatty changes with partial cell necrosis in the liver. A clear reduction in the liver tissue respiration and a decrease in the albumin/globulin ratio in the serum were also observed. Subcutaneous injection of ammonium vanadate (1 mg vanadium/kg body weight per day, for 30 days) caused similar fatty changes in the liver of rats. Intraperitoneal injections of sodium meta-

vanadate (1.25 - 2.5 mg vanadium/kg body weight) in rats caused loss of weight. The toxic effects observed were correlated with the concentration of vanadium in the liver (section 7.2).

9.3.2.4 Effects on the kidney

Data on the effects of vanadium on the human kidney are lacking. Intravenous injection of sodium metavanadate (2.5 - 5 mg/kg body weight) in male dogs resulted in albuminuria. In mice, acute tubular necrosis followed subcutaneous injection of ammonium vanadate at a dose equivalent to 20 mg vanadium/kg body weight. Rats and rabbits inhaling vanadium chloride (70 mg/m^3 2 h/day, for 9 - 12 months) caused fatty changes in the kidney. Vanadate has diuretic and natriuretic effects on the kidney in the rat but not in the dog or cat. Vanadate has also been reported to increase the urinary excretion of calcium, phosphate, bicarbonate, and chloride by the rat kidney. These diuretic and natriuretic effects are thought to be due to the inhibition of Na^+-K^+-ATPase causing inhibition of the tubular reabsorption.

9.3.2.5 Cardiovascular effects

Palpitation of the heart at rest and on exercise has been reported in workers occupationally exposed to vanadium. Transient coronary insufficiency, a high incidence of extra-systoles and bradycardia were reported (section 8.3). Exposure of workers to low levels of vanadium pentoxide (0.2 - 0.5 mg/m^3) did not cause any pathological changes in the blood picture (section 8.4.1).

Electrocardiographic changes (ST-segment depression, increased T-wave amplitudes) were seen after intravenous injection of sodium metavanadate in dogs (2.5 - 5 mg/kg body weight). Long-term inhalation exposure of rats and rabbits to vanadium pentoxide, trioxide, or chloride (10 - 70 mg/m^3, 2 h/day, for 9 - 12 months) caused fatty changes in the myo-cardium as well as perivascular swelling.

9.3.2.6 Pulmonary effects

Asthmatic reactions in conjunction with non-specific bronchial hyperreactivity have occasionally been reported in refinery workers exposed to vanadium pentoxide dust. There has not been any evidence of an immunological mechanism behind such cases. A dose-dependent decline in forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) has been demonstrated in boiler cleaners. The functional increase did not return to normal during the first week following exposure, but fully recovered within one month. The mechanism leading to the obstructive pulmonary impairment has not been clarified.

9.3.2.7 Effects on the immune system

In mice, vanadium and ammonium vanadate affect the normal function of the immune system. Vanadium had slight depressant effects on antibody-forming cells and increased DNA synthesis in splenic leukocytes. Ammonium vanadate increased resistance to E. coli endotoxin, but decreased resistance to Listeria

lethality. In the spleen, it increased the rosetting capability of leukocytes, the formation of megakaryocytes, and red blood cell precursors (section 7.7).

9.3.3 Reproduction, embryotoxicity, and teratogenicity

Human data on the effects of vanadium on reproduction and embryotoxicity are lacking. Vanadium administered to pregnant rats by subcutaneous administration of metavanadate (0.85 mg/kg, equal to 1/20 LD_{50}) accumulated in the placenta. However, the extent to which it reaches the fetus has not been clearly established. During the lactation period, vanadium was found in the mammary glands and was excreted with milk. Morphological changes in spermatozoa as well as desquamation of spermatogenic epithelium in the seminal tubuli were observed. Gonadotoxic effects were suggested by the absence of fertilization of female rats by male rats that had been exposed to 0.85 mg vanadium/kg body weight. The same doses of vanadium given to female rats on the fourth day of pregnancy significantly decreased the number of fetuses (section 7.8.1).

Weanling pigs receiving vanadate (200 mg vanadium/kg body weight) showed a suppressed growth rate and increased mortality. Vanadium was not markedly toxic when fed to growing lambs (200 mg/kg, 84 days) (section 7.8.1).

Tentative results suggest that vanadium is teratogenic for rats and hamsters causing skeletal anomalies and death of the fetuses. Dose-response relationships have not been demonstrated (section 7.8.2). There are no human data concerning possible teratogenic effects of vanadium.

9.3.4 Mutagenicity

The data on the mutagenic potential of vanadium in bacterial systems are inconclusive. There are positive and negative results with E. *coli* and *Salmonella* tests (section 7.9). Data suggest the induction of micronuclei, but not sister chromatid exchange or dominant-lethal mutations. Chromosome effects in vivo and *in vitro* have not been studied.

9.3.5 Carcinogenicity

Life-time studies on mice given 5 µg vanadyl ions/ml as the sulfate in drinking-water did not increase the incidence of

spontaneous tumours and intraperitoneal injections of vanadium(III)2.4pentanedione (24, 60, or 120 mg/kg body weight) did not increase the incidence of lung adenomas in mice. The results of a long-term study on rats with intrabronchiolar implants of vanadium solids were negative. The few studies available do not provide any indications of carcinogenic effects of vanadium (section 7.10).

9.3.6 Risks from exposure of the general population

There are only a few studies on the possible effects of vanadium in ambient air on the general population (section 8.3.2). In one study, air concentrations of vanadium together with 12 other trace elements were found to be correlated with

mortality from pneumonia and lung cancer (coefficients of correlation of 0.443 and 0.347, respectively) and also with mortality from bronchitis (coefficient of correlation of 0.563). In another study, a correlation between the levels of vanadium, cadmium, zinc, tin, and nickel and the incidence of several diseases including "diseases of the heart", "nephritis", and "arteriosclerotic heart" was claimed, but the results of these studies do not establish any causal relationships.

10. RECOMMENDATIONS

There is a conspicuous lack of data on several aspects of the health effects of vanadium compounds. The overwhelming bulk of recent research focuses on the effects of vanadium on biochemical systems, especially specific effects on enzymes, and there are major gaps in knowledge with respect to analytical, metabolic, and exposure data.

There are indications of a weak mutagenic effect of vanadium, but the data are partly conflicting and uncorroborated. Further confirmative mutagenicity studies, including studies on chromosomal effects, should be given high priority. Data on the carcinogenicity of vanadium in various species are practically non-existent. Such studies are urgent and should be conducted as long-term exposure studies.

Vanadium induces toxic effects on the fetus. However, whether these are direct effects or indirect effects resulting from effects of vanadium on the mother is not known. Studies to assess the nature of the teratogenic effects and the mechanism behind them should be encouraged.

Effects resulting from high occupational exposure to vanadium dusts have been reasonably well described. Such exposure levels may cause a variety of clinical manifestations. However, they should be remedied by hygienic and technical improvements. Dose-effect and dose-response relationships have not been well defined at low exposure levels in the range of approximately 0.01 - 0.5 mg/m^3. It is considered important to develop specific indicators for the detection of early adverse effects of vanadium on man.

Epidemiological studies on occupational cohorts, paying particular attention to exposure levels and using proper referent groups, should be encouraged. The literature is inconsistent regarding the documentation of sensitizing properties of vanadium compounds. This is an important aspect with regard to worker protection.

An area of great importance is the exposure of the general population. There are considerable geographical variations in vanadium concentrations in air and water. Epidemiological studies on populations living in areas with high vanadium exposure should be carried out, relating possible adverse effects to exposure levels. Such studies should take into account possible interactions with other pollutants.

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See Also:
Toxicological Abbreviations